WASHINGTON STATE HEALTH CARE AUTHORITY

HTA Draft Appendices: Breast MRI

In Diagnosis and Treatment of Cancer in Women at High Risk

Health Technology Assessment

Date: Friday, June 25, 2010

I. ABBREVIATIONS USED IN THIS DOCUMENT

Other abbreviations, with their explanations, are found, at times in individual critical appraisals and study reviews.

Abbreviation	Definition
ACR	American College of Radiology
ACS	American Cancer Society
BCS	Breast conserving surgery
CBE	Clinical breast exam
CI	Confidence interval
CKD	Chronic kidney disease
CLTR	Cumulative lifetime risk
DCIS	Ductal carcinoma in situ
DM	Digital mammography
ESRD	End stage renal disease
FH	Family history
FN	False negative
FNA	Fine needle aspiration
FP	False positive
FSM	Film screen mammogram
HTA	Health Technology Assessment
HTAP	Health Care Authority's Health Technology Assessment Program
ICDR	Incremental cancer detection rate
IDC	Infiltrating or invasive ductal carcinoma
ILC	Invasive lobular carcinoma
LCIS	Lobular carcinoma in situ
LOE	Level of evidence
MCC	Multicentric cancer
MFC	Multifocal cancer
MRI	Magnetic resonance imaging
MX	Mammography
NA or N/A	Not applicable
NPV	Negative predictive value
NR	Not reported
NS	Not significant
OHSU	Oregon Health Services University
PPV	Positive predictive value
QALY	Quality adjusted life years
RCT	Randomized controlled trial
RD	Absolute risk difference
ROC	Receiver operating curve
RR	Relative risk
SN	Sensitivity
SP	Specificity
SR	Systematic review
TN	True negative
TP	True positive
TP:FP Ratio	True positive to false positive ratio
USPSTF	United States Preventive Services Task Force
WBUS	Whole breast ultrasound
WLE	Wide local excision

II. RATING OF INDIVIDUAL STUDIES AND THE OVERALL QUALITY OF THE EVIDENCE

Delfini Validity & Usability Grading Scale for Summarizing the Evidence for Interventions

Grade of Usability	Strength of Evidence Advice Grades can be applied to individual studies, to conclusions within studies, a body of evidence or to secondary sources such as guidelines or clinical recommendations. General advice is provided below.
Grade A: Useful	The evidence is strong and appears sufficient to use in making health care decisions – it is both valid and useful (e.g., meets standards for clinical significance, sufficient magnitude of effect size, physician and patient acceptability, etc.) Advice: Studies achieving this grade should be outstanding in design, execution and reporting with useful information to aid clinical decision-making, enabling reasonable certitude in drawing conclusions. For a body of evidence: Several well-designed and conducted studies that consistently show similar results • For therapy, screening, prevention and diagnostic studies: RCTs. In some cases a single, large well-designed and conducted RCT may be sufficient; however, without confirmation from other studies results could be due to chance, undetected significant biases, fraud, etc. In such instance the study might receive a Grade A, but the Strength of the Evidence should include a cautionary note. • For natural history and prognosis: Cohort studies
Grade B: Possibly Useful	The evidence appears potentially strong and is probably sufficient to use in making health care decisions - some threats to validity were identified Advice: Studies achieving this grade should be of high quality in design, execution and reporting with non-lethal threats to validity and with sufficiently useful information to aid clinical decision-making, enabling reasonable certitude in drawing conclusions. For a body of evidence: The evidence is strong enough to conclude that the results are probably valid and useful (see above); however, study results from multiple studies are inconsistent or the studies may have some (but not lethal) threats to validity. • For therapy, screening, prevention and diagnostic studies: RCTs. In some cases a single, large well-designed and conducted RCT may be sufficient; however, without confirmation from other studies results could be due to chance, undetected significant biases, fraud, etc. In such instance the study might receive a Grade A, but the Strength of the Evidence should include a cautionary note. • Also for diagnosis, valid studies assessing test accuracy for detecting a condition when there is evidence of effectiveness from valid, applicable RCTs. ▪ For natural history and prognosis: Cohort studies
Grade B-U: Possible to uncertain usefulness	The evidence might be sufficient to use in making health care decisions; however, there remains sufficient uncertainty that the evidence cannot fully reach a Grade B and the uncertainty is not great enough to fully warrant a Grade U. Study quality is such that it appears likely that the evidence is sufficient to use in making health care decisions; however, there are some study issues that raise continued uncertainty. Health care decision-makers should be fully informed of the evidence quality.

Grade U: Uncertain Validity and/or Usefulness	There is sufficient uncertainty that caution is urged regarding its use in making health care decisions. • Uncertain Validity: This may be due to uncertain validity due to methodology (enough threats to validity to raise concern – our suggestion would be to **not** use such a study in most circumstances) or may be due to conflicting results. • Uncertain Usefulness: Or this may be due to uncertain applicability due to results (good methodology, but questions due to effect size, applicability of results when relating to biologic markers, or other issues). These latter studies may be useful and should be viewed in the context of the weight of the evidence. • Uncertain Validity and Usefulness: This is a combination of the above. • Uncertainty of Author: If the author has reached a conclusion that the findings are uncertain, doing a critical appraisal is unlikely to result in a different conclusion. The evidence leaves us uncertain regardless of whether the study is valid or not. Critical appraisal is at the discretion of the reviewer.

AHRQ Risk of Bias Ratings

Overall quality of the evidence was rated by applying the domains recently selected by the Agency for Healthcare Research and Quality (AHRQ) and the Effective Health Care Program (EHCP) group (Owens 09). These domains were selected by AHRQ EHCP after reviewing choices made by the U.S. Preventive Services Task Force (USPSF) (Sawaya 07), the GRADE working group (Guyatt 08) and other evidence-based practice centers (West 02, Treadwell 06). Briefly, The AHRQ EHCP approach assesses the risk of bias, consistency, directness and precision for each outcome or comparison of interest (in some instances, paraphrased below):

AHRQ Overall Risk of Bias Domains

- **Bias** is scored as low, medium, or high risk of bias.
- **Consistency** is the degree of similarity of effect sizes of included studies and is scored as consistent, inconsistent, or unknown/not applicable.
- **Directness** is the linkage between the intervention and health outcomes scored as direct or indirect (meaning intermediate or surrogate outcome measures).
- **Precision** concerns the ability to draw a clinically useful conclusion from the confidence intervals. An imprecise estimate, for example, is one for which the confidence interval is wide enough to include clinically distinct conclusions (e.g., favoring both the interventions being compared).

The overall level of evidence (LOE) for each outcome of interest utilized by the AHRQ and EHCP group includes three grades—high, moderate and inconclusive. For example, if the LOE is high, further research is unlikely to change confidence in the estimate of effect. If evidence is unavailable or does not permit a conclusion, the outcome in the AHRQ EHCP system is graded as inconclusive. For this review, we modified this grading system for overall LOE by adding a fourth category—"borderline" to increase clarity as we believe "moderate" is not precise enough to address evidence of borderline usefulness. We grade the overall LOE as "high" if we find more than one grade B (valid and possibly useful) study reporting consistent results, "moderate" if we find at least one grade B study, "borderline" if we find at least two grade B-U (possible to uncertain validity and usefulness) studies with consistent findings and "inconclusive" if we find single grade B-U studies or grade B-U studies with conflicting results or only grade U studies (uncertain usefulness or validity).

III. APPRAISAL LOCATOR

Number	Abbreviated Reference	Citation	Page
1.	Berg 08	Berg WA, Blume JD, Cormack JB, Mendelson EB, Lehrer D, Böhm-Vélez M, Pisano ED, Jong RA, Evans WP, Morton MJ, Mahoney MC, Larsen LH, Barr RG, Farria DM, Marques HS, Boparai K; ACRIN 6666 Investigators. Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. JAMA. 2008 May 14;299(18):2151-63. Erratum in: JAMA. 2010 Apr 21;303(15):1482. PubMed PMID: 18477782; PubMed Central PMCID: PMC2718688.	9
2.	Brennan 09	Brennan ME, Houssami N, Lord S, Macaskill P, Irwig L, Dixon JM, Warren RM, Ciatto S. Magnetic resonance imaging screening of the contralateral breast in women with newly diagnosed breast cancer: systematic review and meta-analysis of incremental cancer detection and impact on surgical management. J Clin Oncol. 2009 Nov 20;27(33):5640-9. Epub 2009 Oct 5. Review. PubMed PMID: 19805685.	13
3.	Brewer 07	Brewer NT, Salz T, Lillie SE. Systematic review: the long-term effects of false-positive mammograms. Ann Intern Med. 2007 Apr 3;146(7):502-10. Review. PubMed PMID: 17404352.	17
4.	Chen 08	Chen MM, Coakley FV, Kaimal A, Laros RK Jr. Guidelines for computed tomography and magnetic resonance imaging use during pregnancy and lactation. Obstet Gynecol. 2008 Aug;112(2 Pt 1):333-40. PubMed PMID: 18669732.	19
5.	Essink-Bot 06	Essink-Bot ML, Rijnsburger AJ, van Dooren S, de Koning HJ, Seynaeve C. Women's acceptance of MRI in breast cancer surveillance because of a familial or genetic predisposition. Breast. 2006 Oct;15(5):673-6. Epub 2006 Mar 23. PubMed PMID: 16556497.	20
6.	Feig 04	Feig SA. Adverse effects of screening mammography. Radiol Clin North Am. 2004 Sep;42(5):807-19, v. Review. PubMed PMID: 15337417.	22
7.	Fischer 04	Fischer U, Zachariae O, Baum F, et al: The influence of preoperative MRI of the breasts on recurrence rate in patients with breast cancer. EurRadiol 14:1725-1731, 2004.	23
8.	Hoshaw 01	Hoshaw SJ, Klein PJ, Clark BD, Cook RR, Perkins LL. Breast implants and cancer: causation, delayed detection, and survival. Plast Reconstr Surg. 2001 May;107(6):1393-407. PubMed PMID: 11335807.	25
9.	Houssami 08	Houssami N, Ciatto S, Macaskill P, Lord SJ, Warren RM, Dixon JM, Irwig L. Accuracy and surgical impact of magnetic resonance imaging in breast cancer staging: systematic review and meta-analysis in detection of multifocal and multicentric cancer. J Clin Oncol. 2008 Jul 1;26(19):3248-58. Epub 2008 May 12. Review. PubMed PMID: 18474876.	26
10.	Kuhl 10	Kuhl C, Weigel S, Schrading S, Arand B, Bieling H, König R, Tombach B, Leutner C, Rieber-Brambs A, Nordhoff D, Heindel W, Reiser M, Schild HH. Prospective multicenter cohort study to refine management recommendations for women at elevated familial risk of breast cancer: the EVA trial. J Clin Oncol. 2010 Mar 20;28(9):1450-7. Epub 2010 Feb 22. PubMed PMID: 20177029.	29

Number	Abbreviated Reference	Citation	Page
11.	Lee 10	Lee JM, McMahon PM, Kong CY, Kopans DB, Ryan PD, Ozanne EM, Halpern EF, Gazelle GS. Cost-effectiveness of breast MR imaging and screen-film mammography for screening BRCA1 gene mutation carriers. Radiology. 2010 Mar;254(3):793-800. PubMed PMID: 20177093; PubMed Central PMCID: PMC2826703.	33
12.	Lehman 07	Lehman CD, Gatsonis C, Kuhl CK, Hendrick RE, Pisano ED, Hanna L, Peacock S, Smazal SF, Maki DD, Julian TB, DePeri ER, Bluemke DA, Schnall MD; ACRIN Trial 6667 Investigators Group. MRI evaluation of the contralateral breast in women with recently diagnosed breast cancer. N Engl J Med. 2007 Mar 29;356(13):1295-303. Epub 2007 Mar 28. PubMed PMID: 17392300.	35
13.	Lim 10	Lim HI, Choi JH, Yang JH, Han BK, Lee JE, Lee SK, Kim WW, Kim S, Kim JS, Kim JH, Choe JH, Cho EY, Kang SS, Shin JH, Ko EY, Kim SW, Nam SJ. Does pre-operative breast magnetic resonance imaging in addition to mammography and breast ultrasonography change the operative management of breast carcinoma? Breast Cancer Res Treat. 2010 Jan;119(1):163-7. PubMed PMID: 19760039.	38
14.	Lord 07	Lord SJ, Lei W, Craft P, Cawson JN, Morris I, Walleser S, Griffiths A, Parker S, Houssami N. A systematic review of the effectiveness of magnetic resonance imaging (MRI) as an addition to mammography and ultrasound in screening young women at high risk of breast cancer. Eur J Cancer. 2007 Sep;43(13):1905-17. Epub 2007 Aug 2. Review. PubMed PMID: 17681781	39
15.	Mann 10	Mann RM, Loo CE, Wobbes T, Bult P, Barentsz JO, Gilhuijs KG, Boetes C. The impact of preoperative breast MRI on the re-excision rate in invasive lobular carcinoma of the breast. Breast Cancer Res Treat. 2010 Jan;119(2):415-22. PubMed PMID: 19885731.	47
16.	O'Neill 08	O'Neill SM, Rubinstein WS, Sener SF, Weissman SM, Newlin AC, West DK, Ecanow DB, Rademaker AW, Edelman RR. Psychological impact of recall in high-risk breast MRI screening. Breast Cancer Res Treat. 2009 May;115(2):365-71. Epub 2008 Jul 26. PubMed PMID: 18661230.	49
17.	Pengel 09	Pengel KE, Loo CE, Teertstra HJ, Muller SH, Wesseling J, Peterse JL, Bartelink H, Rutgers EJ, Gilhuijs KG. The impact of preoperative MRI on breast-conserving surgery of invasive cancer: a comparative cohort study. Breast Cancer Res Treat. 2009 Jul;116(1):161-9. Epub 2008 Sep 21. PubMed PMID: 18807269.	51
18.	Perazella 07	Perazella MA, Rodby RA. Gadolinium use in patients with kidney disease: a cause for concern. Semin Dial. 2007 May-Jun;20(3):179-85. Review. PubMed PMID: 17555477.	54
19.	Plevritis 06	Plevritis SK, Kurian AW, Sigal BM, Daniel BL, Ikeda DM, Stockdale FE, Garber AM. Cost-effectiveness of screening BRCA1/2 mutation carriers with breast magnetic resonance imaging. JAMA. 2006 May 24;295(20):2374-84. PubMed PMID: 16720823.	55
20.	Sardanelli 04	Sardanelli F, Giuseppetti GM, Panizza P, Bazzocchi M, Fausto A, Simonetti G, Lattanzio V, Del Maschio A; Italian Trial for Breast MR in Multifocal/Multicentric Cancer. Sensitivity of MRI versus mammography for detecting foci of multifocal, multicentric breast cancer in Fatty and dense breasts using the whole-breast pathologic examination as a gold standard. AJR Am J Roentgenol. 2004 Oct;183(4):1149-57. PubMed PMID: 15385322.	57

Number	Abbreviated Reference	Citation	Page
21.	Schwartz 00	Schwartz LM , Woloshin S , Sox HC , Fischhoff B , Welch HG . US women's attitudes to false positive mammography results and detection of ductal carcinoma in situ: cross sectional survey . BMJ 2000 ; 320 : 1635 – 1640.	58
22.	Scomersi 10	Scomersi S, Urbani M, Tonutti M, Zanconati F, Bortul M. Role of magnetic resonance imaging in managing selected women with newly diagnosed breast cancer. Breast. 2010 Apr;19(2):115-9. Epub 2010 Jan 27. PubMed PMID: 20106663.	59
23.	Shellock 06	Shellock FG, Parker JR, Pirovano G, Shen N, Venetianer C, Kirchin MA, Spinazzi A. Safety characteristics of gadobenate dimeglumine: clinical experience from intra- and interindividual comparison studies with gadopentetate dimeglumine. J Magn Reson Imaging. 2006 Dec;24(6):1378-85. Erratum in: J Magn Reson Imaging. 2007 Jul;26(1):217. PubMed PMID: 17078095.	60
24.	Solin 08	Solin LJ, Orel SG, Hwang WT, Harris EE, Schnall MD. Relationship of breast magnetic resonance imaging to outcome after breast-conservation treatment with radiation for women with early-stage invasive breast carcinoma or ductal carcinoma in situ. J Clin Oncol. 2008 Jan 20;26(3):386-91. PubMed PMID: 18202414	61
25.	Taneja 09	Taneja C, Edelsberg J, Weycker D, Guo A, Oster G, Weinreb J. Cost effectiveness of breast cancer screening with contrast-enhanced MRI in high-risk women. J Am Coll Radiol. 2009 Mar;6(3):171-9. PubMed PMID: 19248993.	64
26.	Turnbull 10	Turnbull L, Brown S, Harvey I, Olivier C, Drew P, Napp V, Hanby A, Brown J. Comparative effectiveness of MRI in breast cancer (COMICE) trial: a randomised controlled trial. Lancet. 2010 Feb 13;375(9714):563-71. PubMed PMID: 20159292.	66
27.	Warner 08	Warner E, Messersmith H, Causer P, Eisen A, Shumak R, Plewes D. Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer. Ann Intern Med. 2008 May 6;148(9):671-9. Review. PubMed PMID: 18458280.	71
28.	Warren 09	Warren R, Ciatto S, Macaskill P, Black R, Houssami N. Technical aspects of breast MRI--do they affect outcomes? Eur Radiol. 2009 Jul;19(7):1629-38. Epub 2009 Feb 27. Review. PubMed PMID: 19247664.	77
29.	Weinstein 09	Weinstein SP, Localio AR, Conant EF, Rosen M, Thomas KM, Schnall MD. Multimodality screening of high-risk women: a prospective cohort study. J Clin Oncol. 2009 Dec 20;27(36):6124-8. Epub 2009 Nov 2. PubMed PMID: 19884532; PubMed Central PMCID: PMC2793033.	78

IV. CRITICAL APPRAISAL DOCUMENTATION

Berg 08
MRI: Screening
Citation: Berg WA, Blume JD, Cormack JB, Mendelson EB, Lehrer D, Böhm-Vélez M, Pisano ED, Jong RA, Evans WP, Morton MJ, Mahoney MC, Larsen LH, Barr RG, Farria DM, Marques HS, Boparai K; ACRIN 6666 Investigators. Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. JAMA. 2008 May 14;299(18):2151-63. Erratum in: JAMA. 2010 Apr 21;303(15):1482. PubMed PMID: 18477782; PubMed Central PMCID: PMC2718688.
Manufacture Involvement: No
Reviewer Grade:
Delfini Grade: BU
AHRQ Grade: Medium Risk of Bias

Delfini Evidence Statement:
The evidence might be sufficient to use in making health care decisions; however, there remains sufficient uncertainty that the evidence cannot fully reach a Grade B and the uncertainty is not great enough to fully warrant a Grade U. Study quality is such that it appears likely that the evidence is sufficient to use in making health care decisions; however, there are some study issues that raise continued uncertainty. Health care decision-makers should be fully informed of the evidence quality.

PUBLISHED ABSTRACT SECTIONS (WHITE) WITH REVIEWER COMMENTS & KEY POINTS OF STUDY (RC IN GREY)
CONTEXT: Screening ultrasound may depict small, node-negative breast cancers not seen on mammography.
OBJECTIVE: To compare the diagnostic yield, defined as the proportion of women with positive screen test results and positive reference standard, and performance of screening with ultrasound plus mammography vs mammography alone in women at elevated risk of breast cancer.
DESIGN, SETTING, AND PARTICIPANTS: From April 2004 to February 2006, 2809 women, with at least heterogeneously dense breast tissue in at least 1 quadrant, were recruited from 21 sites to undergo mammographic and physician-performed ultrasonographic examinations in randomized order by a radiologist masked to the other examination results. Reference standard was defined as a combination of pathology and 12-month follow-up and was available for 2637 (96.8%) of the 2725 eligible participants.
RC: Authors remark upon concerns about generalizability of prior studies of screening with ultrasound. They address some limitations of ultrasound screening at the date of their writing. They, comment on the lack of standardized screening protocols and point out that, "There is concern for the operator dependence of freehand screening breast ultrasound because an abnormality must be perceived while scanning for it to be documented." They also add that, studies have shown that "consistent breast ultrasound examination performance and interpretation is possible with minimal training." They address these issues in their study by having standardization and utilizing radiologist investigators who were tested for their skills.
MAIN OUTCOME MEASURES: Diagnostic yield, sensitivity, specificity, and diagnostic accuracy (assessed by the area under the receiver operating characteristic curve) of combined mammography plus ultrasound vs mammography alone and the positive predictive value of biopsy recommendations for mammography plus ultrasound vs mammography alone.
RC: ▪ Observational study ▪ Prospective ▪ Multi-center ▪ Standardized protocol and interpretive criteria used ▪ Blind assessment ▪ Intermediate marker studied; mortality was not an endpoint **Population** ▪ At least 25 years of age — mean age at enrollment was 55 (range 25 to 91 years) ▪ At elevated risk (including personal history of breast cancer, prior atypical biopsy, and elevated risk by Gail or Claus models or both) presenting for routine annual mammogram as determined by study personnel and had

heterogeneously dense or extremely dense parenchyma in at least 1 quadrant by prior mammography findings.
- Exclusions included women with signs of breast cancer, recent screening, with implants, pregnant, lactating, planning to become pregnant within 2 years or women with known metastatic disease unless disease-free for 5 years or more
- Of 2725 women, 2712 (99.5%) women underwent imaging using both modalities and 2637 comprised the reference set (96.8%)

Intervention
- All patients received both mammographic and ultrasound screening
- Sequence of performance of mammography and ultrasound were randomized. No details of how randomization was done except to provide stratification information.
- At least 2-view mammography was performed using either screen-film or digital mammography
- Visually estimated mammography was recorded
- Computer-assisted detection was not permitted
- Survey ultrasound was performed using high-resolution linear array, broad bandwidth transducers with maximum frequency of at least 12 MHz, with scanning in transverse and sagittal planes. Lesions other than simple cysts were imaged with and without spatial compounding and power or color Doppler in orthogonal planes (typically radial and antiradial orientations). An image (with embedded clock time) was recorded on entering the ultrasound suite, at the beginning and end of ultrasonographic screening, and on leaving the suite to determine the time to scan and the total physician time in the room. Electively, the axilla could be scanned, and its inclusion was recorded. Investigators recorded ultrasonographic background echotexture and lesion features using Breast Imaging and Reporting Data System (BI-RADS): Ultrasound descriptors and average breast thickness to the nearest centimeter.
- Recommendations for additional imaging were "separately" allowed.
- If the recommendation from the study mammography or ultrasound was for other than routine annual screening, an integrated mammography plus ultrasound interpretation was recorded by a qualified site investigator radiologist. Otherwise, if both ultrasound and mammography were interpreted as negative or benign, no separate integrated interpretation was performed, and the combination of mammography plus ultrasound was assumed to be negative.
- Each lesion and breast was assessed using BI-RADS, however, a BI-RADS score of 0 was not used to allow for meaningful receiver operator characteristic (ROC) analysis.
- Investigators were also asked to rate likelihood of malignancy from 0% to 100% to provide a scale that would potentially improve the ROC analysis.
- Recommendations for routine annual follow-up, short interval follow- up in 6 months, additional imaging, and biopsy were recorded separately from assessments.
- Investigators separately analyzed results based on recommendations, with additional imaging or biopsy or both considered positive and short interval or routine follow-up considered negative.

Reference Standard
- Combination of biopsy results within 365 days and clinical follow-up at 1 year

Definitions
- Authors defined elevated risk using a variety of criteria, including personal history of breast cancer, prior atypical biopsy, and elevated risk by Gail or Claus models or both.
- The absence of a known diagnosis of cancer on a participant interview, review of medical records at the 1-year screening follow-up, or both was considered disease negative, as were 3 cases with double prophylactic mastectomies.
- Biopsy results showing cancer (in situ or infiltrating ductal carcinoma, or infiltrating lobular carcinoma) in the breast or axillary lymph nodes were considered malignant, disease positive, as was 1 other invasive cancer, which proved to be a case of melanoma metastatic to axillary lymph nodes. The melanoma case was retained in the analysis because of its classification at the time the database was locked for analysis.
- The primary unit of analysis is the participant, with the most severe breast imaging assessment on mammography or on mammography plus ultrasound used as the primary end point.
- A BI-RADS assessment of 4a, 4b, 4c, or 5 was considered positive (seen and suspicious) for the mammographic or ultrasonographic imaging test or combination of tests, and an assessment of BI-RADS 1, 2, or 3 was considered negative, as is standard in audits of mammographic outcomes.

RESULTS: Forty participants (41 breasts) were diagnosed with cancer: 8 suspicious on both ultrasound and mammography, 12 on ultrasound alone, 12 on mammography alone, and 8 participants (9 breasts) on neither. The diagnostic yield for mammography was 7.6 per 1000 women screened (20 of 2637) and increased to 11.8 per 1000 (31

of 2637) for combined mammography plus ultrasound; the supplemental yield was 4.2 per 1000 women screened (95% confidence interval [CI], 1.1 to 7.2 per 1000; P = .003 that supplemental yield is 0). The diagnostic accuracy for mammography was 0.78 (95% CI, 0.67 to 0.87) and increased to 0.91 (95% CI, 0.84 to 0.96) for mammography plus ultrasound (P = .003 that difference is 0). Of 12 supplemental cancers detected by ultrasound alone, 11 (92%) were invasive with a median size of 10 mm (range, 5 to 40 mm; mean [SE], 12.6 [3.0] mm) and 8 of the 9 lesions (89%) reported had negative nodes. The positive predictive value of biopsy recommendation after full diagnostic workup was 19 of 84 for mammography (22.6%; 95% CI, 14.2% to 33%), 21 of 235 for ultrasound (8.9%, 95% CI, 5.6% to 13.3%), and 31 of 276 for combined mammography plus ultrasound (11.2%; 95% CI. 7.8% to 15.6%).

CONCLUSIONS: Adding a single screening ultrasound to mammography will yield an additional 1.1 to 7.2 cancers per 1000 high-risk women, but it will also substantially increase the number of false positives.

RC:

- Authors remark that DCIS is difficult to see on ultrasound.
- Authors acknowledge that the use of the Gail and Claus models to calculate risk may have affected the racial distribution of participants as the Gail model is known to underestimate risk in African Americans.
- Authors state that, "There appears to be no role for screening ultrasound in women undergoing screening MRI, even though ultrasound may be helpful in guiding biopsy of suspicious findings seen first on MRI. Ultrasound may be more appropriate than MRI for screening women of intermediate risk due to its reduced cost relative to MRI. Many of the cancers seen only on MRI are small, node negative invasive cancers. Unlike ultrasound, MRI readily depicts DCIS, although DCIS remains overrepresented among false-negative MRI examinations. It is uncertain whether detection of DCIS is required or whether detection of node-negative invasive breast cancer is sufficient for a screening test. It will be important to see the stage distribution of breast cancers in subsequent rounds of screening with mammography plus ultrasound in this study and to know how many invasive cancers will be seen only on MRI at the 24- month time point."
- Authors state that, "Ultrasound is well tolerated, the technology is widely available, and it does not require intravenous contrast material. If, however, screening ultrasound is to be widely implemented, several major issues remain. First, it will be very important to know the role of annual screening ultrasound in addition to mammography, and such a study is in progress with participants in this protocol. The time to perform bilateral screening ultrasound is problematic, at a median of 19 minutes. This does not include comparison to prior studies, discussion of results with patients, nor creation of a final report, although the time may be artificially prolonged by protocol requirements to measure each lesion other than a simple cyst in 2 planes and to fully characterize each such lesion with and without spatial compounding and with and without color or power Doppler. Nineteen minutes is considerably longer than the average 4 minutes 39 seconds reported by Kolb et al for physicians scanning or the average 10 minutes reported by Kaplan for technologists. Currently, there is only a single billing code for breast ultrasound (current procedural terminology code 76645), and Medicare global reimbursement is $85 in 2008, which does not fully cover the costs of performing and interpreting the examination. Outcomes similar to those of our physician-performed study have been reported with technologist-performed ultrasound, and specialized training of technologists is encouraged to counter a current shortage of qualified physician and technologist personnel. Further validation of technologist performed screening breast ultrasound is encouraged. Automated whole breast ultrasound may facilitate implementation and profitability of screening ultrasound but will result in hundreds of images to be reviewed and stored, with attendant increased capital and professional costs and potential increased malpractice exposure; validation of such methods is needed. The full costs of screening breast ultrasound in this protocol, including the costs of induced additional testing and biopsy, are being analyzed and reported separately. The final barrier to implementing screening ultrasound is the risk of false positive results. The performance characteristics of mammography were within accepted ranges (10.5% recalled for additional imaging or biopsy; 3.2% of participants biopsied after full workup, with 23% proving malignant; 2.2% recommended for short interval follow-up). We observed a 5.4% recall rate for ultrasound (142 of 2637 recommended for additional imaging), which may be artificially low in this series because physicians performed the screening ultrasound and could directly evaluate lesions in real-time. Of 2637 participants, 233 (8.8%) participants had findings considered suspicious on ultrasound with 136 participants having suspicious findings on ultrasound but not mammography and prompting biopsy, and 235 participants (8.9%) were recommended for biopsy based on ultrasound after full workup. Only 20 of 233 (8.6%) of participants with suspicious ultrasonographic findings—12 (8.8%) of 136 of those with suspicious findings biopsied based on ultrasound alone—and 21 of 235 (8.9%) of participants whose lesions were recommended for biopsy based on ultrasound proved to have cancer. The 8.8% to 8.9% PPV of biopsies prompted by ultrasound in our study is similar to the 11% rate seen across prior series. Diagnostic uncertainty for complicated cysts remains a major source of false

positive results, with 43 participants undergoing only cyst aspiration included among those with a suspicious finding on ultrasound. Elastography, in which the deformability of the mass is assessed during ultrasound, can help distinguish complicated cysts from suspicious solid masses and should reduce this source of false positives. Another 227 participants (8.6%) were recommended for short interval follow- up based on ultrasound, similar to the 6.3% rate across other series. Whether the risk of false-positive results with ultrasound will diminish in our study population with subsequent screening rounds, as has been seen with mammography and in small series with both ultrasound and MRI is under evaluation. We have been separately quantifying patient anxiety and discomfort (ie, "process utility") induced by addition of screening ultrasound." [References omitted.]

- AUTHORS' CONCLUSION" "The addition of a single screening ultrasonographic examination to mammography for women at elevated risk of breast cancer results in increased detection of breast cancers that are predominantly small and node-negative. We defined elevated risk using a variety of criteria, including personal history of breast cancer, prior atypical biopsy, and elevated risk by Gail or Claus models or both. Recent literature suggests that any combination of factors that confers 3-fold relative risk compared with women without the risk factor would be "high risk," including dense breast tissue.9 Across all series to date, over 90% of cancers seen only on ultrasound have been in women with more than 50% dense breast tissue, although 3 of 12 cancers (25%) seen only on ultrasound in this series were in women with only 26% to 40% dense breast tissue (as visually estimated), suggesting that women with other risk factors may benefit from screening ultrasound even if their breast tissue is less dense. The age at which to begin screening women at increased risk would reasonably derive from the age at which the risk of breast cancer is equal to that for an average woman aged 40 or 50 years, depending on national policy. The detection benefit of a single screening ultrasound in women at elevated risk of breast cancer is now well validated. However, it comes with a substantial risk of false-positive results (ie, biopsy with benign results and/or short interval follow-up). Our results should be interpreted in the context of recent guidelines recommending annual MRI in women at very high risk of breast cancer. Importantly, evaluation of annual (incidence) screening ultrasound is continuing in ACRIN 6666, as is evaluation of a single screening MRI in these women."

Brennan 09

Study Reference: Brennan ME, Houssami N, Lord S, Macaskill P, Irwig L, Dixon JM, Warren RM, Ciatto S. Magnetic resonance imaging screening of the contralateral breast in women with newly diagnosed breast cancer: systematic review and meta-analysis of incremental cancer detection and impact on surgical management. J Clin Oncol. 2009 Nov 20;27(33):5640-9. Epub 2009 Oct 5. Review. PubMed PMID: 19805685.

Abstract

Purpose

Preoperative magnetic resonance imaging (MRI) is increasingly used for staging women with breast cancer, including screening for occult contralateral cancer. This article is a review and meta-analysis of studies reporting contralateral MRI in women with newly diagnosed invasive breast cancer.

Methods

We systematically reviewed the evidence on contralateral MRI, calculating pooled estimates for positive predictive value (PPV), true-positive:false-positive ratio (TP:FP), and incremental cancer detection rate (ICDR) over conventional imaging. Random effects logistic regression examined whether estimates were associated with study quality or clinical variables.

Results

Twenty-two studies reported contralateral malignancies detected only by MRI in 131 of 3,253 women. Summary estimates were as follows: MRI-detected suspicious findings (TP plus FP), 9.3% (95% CI, 5.8% to 14.7%); **ICDR, 4.1%** (95% CI, 2.7% to 6.0%), **PPV, 47.9% (95% CI, 31.8% to 64.6%);** TP:FP ratio, 0.92 (95% CI, 0.47 to 1.82). PPV was associated with the number of test positives and baseline imaging. **Few studies included consecutive women, and few ascertained outcomes in all subjects.** Where reported, 35.1% of MRI-detected cancers were ductal carcinoma in situ (mean size = 6.9 mm), 64.9% were invasive cancers (mean size = 9.3 mm), and the majority were stage pTis or pT1 and node negative. Effect on treatment was inconsistently reported, but **many women underwent contralateral mastectomy**.

Conclusion

MRI detects contralateral lesions in a substantial proportion of women, but **does not reliably distinguish benign from malignant findings.** Relatively high ICDR may be due to selection bias and/or overdetection. Women must be informed of the uncertain benefit and potential harm, including additional investigations and surgery. *J Clin Oncol 27:5640-5649*.

Reviewer Evidence Rating: Grade BU

AHRQ Risk of Bias Rating: Medium risk of bias

Delfini Evidence Statement:

The evidence might be sufficient to use in making health care decisions; however, there remains sufficient uncertainty that the evidence cannot fully reach a Grade B and the uncertainty is not great enough to fully warrant a Grade U. Study quality is such that it appears likely that the evidence is sufficient to use in making health care decisions; however, there are some study issues that raise continued uncertainty. Health care decision-makers should be fully informed of the evidence quality.

Reviewer Comment:

- MRI does not differentiate well between benign and malignant findings in the contralateral breast in women with newly diagnosed breast cancer – the majority of women with suspicious MRI lesions were false positive tests.
    - Unintended consequences might include: anxiety, additional unnecessary investigations, mastectomies or other interventions, delay in surgery of ipsilateral breast cancer.
- Sensitivity and specificity are not known because cancer outcomes could not be ascertained in subjects with negative MRIs.

- The high percentage of DCIS (35%) suggests that some of the additional MRI-only detected lesions are of low malignant potential.
- The only currently available study of long-term follow-up in women having preoperative MRI found no significant difference in the 8-year rates of clinical breast cancer relative to women who did not have preoperative MRI (Solin 08).

- The effectiveness of a screening test is demonstrated by showing that it reduces patient mortality. If there is evidence that it detects an increased number of cases of disease with a reduction in rates of interval cancers or the incidence of advanced cancers in subsequent screening rounds it may be reasonable to conclude that the evidence is suggestive of efficacy. This meta-analysis did not assess the impact of MRI screening on any of these outcomes. Therefore conclusions about the efficacy of MRI as a screening test in women with recently diagnosed invasive breast cancer must based on evidence of increased breast cancer case findings together with assumptions about the benefits of early detection, considering that clinical benefits may not outweigh harms if, for example chemotherapy would have reduced or eliminated risk of death from the detected cancers. Women with newly diagnosed breast cancer should be thoroughly informed about the possibility of false positive tests and the increased risk for further interventions such as recall for repeat testing, biopsy and other surgical interventions if they undergo contralateral breast MRI. The only currently available follow-up study of women with newly diagnosed invasive breast cancer undergoing contralateral breast MRI found no significant difference in the 8-year rates of clinical breast cancer relative to women who did not have preoperative MRI (Solin 08).

Study Type

Meta-analysis of studies reporting contralateral MRI in women with newly diagnosed invasive breast cancer.

Funding Source

Supported in part by National Health and Medical Research Council Program Grant No. 402764 to Screening and Test Evaluation Program. J.M.D. is supported by Breakthrough Breast Cancer.

Aim

Details	To provide pooled estimates for positive predictive value (PPV), true-positive:false-positive ratio (TP:FP), and incremental cancer detection rate (ICDR) for contralateral MRI in women with newly diagnosed invasive breast cancer over conventional imaging.

Outcome Measures

Details	See Methods Systematic Review

Population and N

Twenty-two studies were eligible for inclusion, reporting CBCs in 137 of 3,253 women. These consisted of 18 studies reporting 123 MRI-detected CBCs (and six malignancies occult to MRI) in 3,147 women with index lesions that included invasive ductal, invasive lobular, and other invasive tumors (group 1) and four studies reporting eight MRI-detected CBCs in 106 women with only ILC as the index lesion (group 2)/ There were 11 prospective studies, 10 retrospective studies, and one study that did not report design. There were no randomized trials of MRI in this setting. Baseline imaging consisted of mammography alone or mammography with ultrasound, but eight studies did not specify baseline imaging.

Inclusion Criteria For Studies

	See methods Secondary Study

::SECONDARY STUDY

Search Strategy

Details	Medline 1950 through March 2008
	▪ No remarks

Selection and Critical Appraisal Methods

	Inclusion criteria were as follows: (1) studies of preoperative MRI in women with suspected or proven invasive breast cancer reporting contralateral findings relative to the index cancer, which (2) provided data for both true-positive (TP) and false-positive (FP) detection in the contralateral breast as a minimum measure of accuracy. Because this review aimed to determine the incremental benefit of MRI (its ability to detect cancer above what has been identified on clinical and imaging evaluation), subjects with CBC detected or suspected on clinical and/or conventional imaging assessment were excluded (38 subjects in 10 studies). Studies not histologically verifying the majority of MRI-detected abnormalities were ineligible for inclusion. For each study, positive predictive value (PPV; TP/[TP + FP]), TP:FP ratio, incremental cancer detection rate (ICDR; TP/[TP+FP+TN+FN]), and overall proportion with positive MRI findings (POS; [TP + FP]/[TP + FP+TN+FN]) were computed.

Combining Results

	See Methods above

Heterogeneity for Meta-analyses

	Yes. Details not reported

Weighting

	▪ No

Sensitivity Analysis

	▪ Yes, similar results when analyzed by prospective vs retrospective data

Diagnostic Issues

	• No mention of blinding • Only 3 studies included a consecutive cohort • Some lost data and patients without MRI and reference test

Screening

Threat	Problems identified
Threat	▪ There is no evidence that early diagnosis and treatment will improve outcomes compared to later diagnosis and treatment

Blinding

	▪ No mention of blinding

Missing Values in Results

	Yes. Total missing not stated.

Meta-Analysis Results

Measures of Test Function:
On the basis of the 18 studies in group 1, the pooled estimate for detecting a suspicious- appearing MRI abnormality occult to conventional imaging (MRI positives:TP and FP) was 9.3% (95% CI, 5.8% to 14.7%), with an interquartile range (IQR) of 3.8% to 13.9%. Study specific PPV ranged from 17% to 100% (IQR, 29% to 100%). The summary estimate of PPV was 47.9% (95% CI, 31.8% to 64.6%). The corresponding summary TP:FP ratio was 0.92 (95% CI, 0.47 to 1.82). The PPV and TP:FP ratio did not vary by study quality (including whether the study design was prospective or retrospective) or cancer prevalence.

Tumor Type:
Tumor type was reported for 114 of 123 MRI-detected CBCs reported in group 1 (index lesion any histologic type), showing that 35.1% (40 of 114) were pure ductal carcinoma in situ (DCIS), and 64.9% (74 of 114) were invasive cancers. Individual tumor size was reported for 43 of the 123 MRI-detected CBCs in group 1. For DCIS (18 tumors), mean tumor size was 6.9mm(median, 5.5 mm; IQR, 4 to 8 mm; range, 1 to 25 mm), and invasive cancers (25 tumors in four studies) had a mean tumor size of 9.3mm(median, 9 mm; IQR, 7 to 10 mm; range, 3 to 17 mm). Both tumor type and size of individual lesions was not reported in any of the studies in group 2 (index lesion of ILC only).

Brewer 07
Psychological Impacts Surrounding Use of MRI for Women with Breast Cancer or at High-risk of Breast Cancer
Systematic Review
Citation: Brewer NT, Salz T, Lillie SE. Systematic review: the long-term effects of false-positive mammograms. Ann Intern Med. 2007 Apr 3;146(7):502-10. Review. PubMed PMID: 17404352.
Manufacture Involvement: No
Reviewer Grade
Delfini Grade: BU
AHRQ Grade: Medium Risk of Bias

Delfini Evidence Statement:
The evidence might be sufficient to use in making health care decisions; however, there remains sufficient uncertainty that the evidence cannot fully reach a Grade B and the uncertainty is not great enough to fully warrant a Grade U. Study quality is such that it appears likely that the evidence is sufficient to use in making health care decisions; however, there are some study issues that raise continued uncertainty. Health care decision-makers should be fully informed of the evidence quality.

PUBLISHED ABSTRACT SECTIONS WITH REVIEWER COMMENTS (RC)
BACKGROUND: Although abnormal screening mammograms deleteriously affect the psychological well-being of women during the time immediately surrounding the tests, their long-term effects are poorly understood.
RC: Specific to mammography, but seems reasonable that findings could be applicable to MRI
PURPOSE: To characterize the long-term effects of false-positive screening mammograms on the behavior and well-being of women 40 years of age or older.
RC: Population characteristics: **Women 40 years of age and older undergoing routine mammography**
DATA SOURCES: English-language studies from the MEDLINE, Web of Science, EMBASE, CINAHL, PsycINFO, and ERIC databases through **August 2006**.
RC: The search terms were (false positive OR abnormal OR benign) AND (breast cancer OR mammog*). Manual searches also performed.
STUDY SELECTION: Studies were identified that examined the effects of false-positive results of routine screening mammography on women's behavior, well-being, or beliefs.
RC: It was required that women receiving false-positive results be compared with women from the same sample who received normal results. Authors were interested in avoiding groups with unscreened women or women screened at other times or in different settings. It was required that outcome measures be assessed at least 1 month after cancer was ruled out so that the data reflected long-term consequences of false-positive screening results and not immediate distress in the period between receiving an abnormal test result and the subsequent negative result for cancer.
DATA EXTRACTION: Two investigators independently coded study characteristics, quality, and effect sizes.
DATA SYNTHESIS: 23 eligible studies (n = 313,967) were identified. A random-effects meta-analysis showed that U.S. women who received false-positive results on screening mammography were more likely to return for routine screening than those who received normal results (risk ratio, 1.07 [95% CI, 1.02 to 1.12]). The effect was not statistically significant among European women (risk ratio, 0.97 [CI, 0.93 to 1.01]), and Canadian women were less likely to return for routine screening because of false-positive results (risk ratio, 0.63 [CI, 0.50 to 0.80]). Women who received false-positive results conducted more frequent breast self-examinations and had higher, but not apparently pathologically elevated, levels of distress and anxiety and thought more about breast cancer than did those with normal results.
RC: As findings appear to be culturally-related, **a change in US culture could render findings no longer current**. Other findings are reported by the authors as a narrative review as few studies assessed their outcomes of interest and because of wide heterogeneity of assessment methods. Many of these findings were completely mixed among studies. Key among these include — Psychological Distress: ▪ Of 9 studies reviewed—

- 4 studies = statistically significant greater symptoms of distress
- 3 studies = non-significant findings (could be power issue)
- 2 studies = mixed results

Anxiety:
- Of 11 studies reviewed—
- 4 = stat sig higher levels of anxiety
- 4 = no effect (could be power issue)
- 3 = mixed

Depression:
- Of 9 studies reviewed—
- 1 study found lower levels of depression
- 7 reported no effect (could be power issue)
- 1 reported mixed findings

Authors' conclusion is that "The pattern of results suggests no long-term symptoms of depression in women who receive false-positive mammograms."

LIMITATIONS: Correlational study designs, a small number of studies, a lack of clinical validation for many measures, and possible heterogeneity.

RC: No performance of critical appraisal was reported, however, authors did appear to look closely at use of standardized instruments. The authors also state that, "The published studies that we reviewed may represent a biased subset of studies conducted, or they may have had selective reporting of outcomes."

CONCLUSIONS: Some women with false-positive results on mammography may have differences in whether they return for mammography, occurrence of breast self-examinations, and levels of anxiety compared with women with normal results. Future research should examine how false-positive results on mammography affect other outcomes, such as trust and health care use.

RC: Based on this study the **evidence is insufficient for concluding meaningful psychological harm in women with false positive tests from mammography who are at average risk of breast cancer**.

Chen 08 (from reference review)

Reference	Abstract	Comments
Chen MM, Coakley FV, Kaimal A, Laros RK Jr. Guidelines for computed tomography and magnetic resonance imaging use during pregnancy and lactation. Obstet Gynecol. 2008 Aug;112(2 Pt 1):333-40. PubMed PMID: 18669732.	There has been a substantial increase in the use of computed tomography (CT) and magnetic resonance imaging (MRI) in pregnancy and lactation. Intravenous gadolinium is contraindicated and should be used only when absolutely essential. It seems to be safe to continue breast-feeding immediately after receiving iodinated contrast or gadolinium. When used appropriately, CT and MRI can be valuable tools in imaging pregnant and lactating women; risks and benefits always should be considered and discussed with patients. The 2007 American College of Radiology guidance document for safe MRI practices recommended that intravenous gadolinium should be avoided during pregnancy and should be used only if absolutely essential and that the risks and benefits of gadolinium use be discussed with the pregnant patient and referring clinicians. Gadolinium is classified as a category C drug by the U.S. Food and Drug Administration and can be used if considered critical (only to be administered "if the potential benefit justifies the potential risk to the fetus").	Guideline Delfini evidence grade: Grade U AHRQ Rating of Bias: High

Essink-Bot 06

Psychological Impacts Surrounding Use of MRI for Women with Breast Cancer or at High-risk of Breast Cancer

Citation: Essink-Bot ML, Rijnsburger AJ, van Dooren S, de Koning HJ, Seynaeve C. Women's acceptance of MRI in breast cancer surveillance because of a familial or genetic predisposition. Breast. 2006 Oct;15(5):673-6. Epub 2006 Mar 23. PubMed PMID: 16556497.

Manufacture Involvement: No disclosures

Reviewer Grade

Delfini Grade: BU

AHRQ Rating: Medium risk of bias

Delfini Evidence Statement:

The evidence might be sufficient to use in making health care decisions; however, there remains sufficient uncertainty that the evidence cannot fully reach a Grade B and the uncertainty is not great enough to fully warrant a Grade U. Study quality is such that it appears likely that the evidence is sufficient to use in making health care decisions; however, there are some study issues that raise continued uncertainty. Health care decision-makers should be fully informed of the evidence quality.

PUBLISHED ABSTRACT SECTIONS WITH REVIEWER COMMENTS (RC)

Magnetic resonance imaging (MRI) of the breasts is a promising screening modality for early detection in women at increased breast cancer risk. We investigated the subjective experiences with MRI and the preferences for MRI, mammography or clinical breast examination in 178 high-risk women adhering to a breast cancer surveillance programme. MRI was reported to cause limited discomfort. About 44% preferred MRI as a screening test (mammography: 14%). MRI provided the most reassurance of breast cancer being absent in case of a favourable test result. MRI seems to be acceptable as a screening test for women at increased breast cancer risk and is preferred by them over mammography.

RC: Population notes: Women with >15% cumulative lifetime risk (CLTR) are screened by biannual CBE and annual imaging by mammography and MRI. A study on the psychological and health-status effects of screening, including the present substudy on subjective participant burden of MRI, was performed using a consecutive sample undergoing MRI at single site at a family practice cancer clinic in a university setting in the Netherlands. Women ranging in age from 25 to 60, mean age 42.8 years. Authors reported that, "About 15.1% (27/179) of the women had a CLTR of developing breast cancer of >50% because of an identified BRCA1/2 mutation, 53.6% (96/179) had an assigned CLTR of 30 to 50% and 31.3% (56/179) a CLTR of 15 to 30%. About 83.7% (149/178) of the participants had undergone (a) previous MRI scan(s) for early detection of breast cancer (56/178, 1 previous MRI; 86/178, 2 or more previous MRIs; 7/ 178, number unknown)."

Authors state that, "We recognise that our results may be affected by the fact that women with previous adverse experiences with MRI scanning who decided not to have a further MRI were not included in this study. However, in the total sample of the MRISC study, only 4.7% of women adhering to surveillance refused further screening by MRI because of claustrophobia or similar reasons… This seems similar to the observation in the UK study, where 'such reasons for withdrawal' were reported to be 'rare'.[Leach MO, Boggis CR, Dixon AK, Easton DF, Eeles RA, Evans DG, et al. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). Lancet 2005;365(9473):1769–78.]" They also state that, "Though not directly comparable, the study reported by Liang et al. also suggests that MRI is preferred over routine mammography [Liang W, Lawrence WF, Burnett CB, Hwang YT, Freedman M, Trock BJ, et al. Acceptability of diagnostic tests for breast cancer. Breast Cancer Res Treat 2003;79(2):199–206.]"

Methods notes:

- Questionnaire administered in morning before scan and another 1 week later. Both addressed discomfort with timing of MRI in menstrual cycle and worry. Women were asked to state preference for either clinical breast exam (CBE), mammography or MRI "…under the assumption that all screening modalities 'performed equally well in a medical sense'; and the level of reassurance they expected to experience from each test, assuming a favourable result (no abnormalities)."
- There is no information as to whether the instrument used was validated or used in other research.

Loss:

Of 182 women invited—
- 178 completed questionnaires prior to scan (97.8%)
- 176 completed both (96.7%)

Reported Results:
- Discomfort associated with seven aspects of undergoing MRI scanning were reported. However, the authors reported the following—
- "Assuming equal performance in a medical sense, 44.4% (75/169) expressed a preference for MRI as a screening test, 41.4% (70/169) for CBE and 14.2% (24/169) for mammography. Further, 64.4% (114/177) reported that they would feel completely reassured by a favourable MRI result, whereas this was 40.1% (71/177) for mammography and 27.8% (49/177) for CBE, respectively."

Conclusions: Authors conclude that, "…MRI is acceptable as screening modality for most women at significantly increased breast cancer risk due to a genetic or familial predisposition, and is preferred by them over mammography."

Dutch study may not be applicable to US population as "acceptance" could have cultural variation. Yet evidence is suggestive of acceptability of MRI by a population that is similar prognostically.

Feig 04
Psychological Impacts Surrounding Use of MRI for Women with Breast Cancer or at High-risk of Breast Cancer
Citation: Feig SA. Adverse effects of screening mammography. Radiol Clin North Am. 2004 Sep;42(5):807-19, v. Review. PubMed PMID: 15337417.
Manufacture Involvement: No information
Reviewer Grade
Delfini Grade: U
AHRQ Grade: High risk of bias

Delfini Evidence Statement:
There is sufficient uncertainty that caution is urged regarding its use in making health care decisions.

PUBLISHED ABSTRACT SECTIONS (WHITE) WITH REVIEWER COMMENTS & KEY POINTS OF STUDY (RC IN GREY)
The main risks and other adverse consequences from screening mammography include discomfort from breast compression, patient recall for additional imaging, and false positive biopsies. Although these risks affect a larger number of women than those who benefit from screening, the risks are less consequential than the life-sparing benefits from early detection. Radiation risk, even for multiple screenings, is negligible at current mammography doses. Anxiety before screening or resulting from supplementary imaging work-up, short-term follow-up, cyst aspiration, and biopsy has not dampened the enthusiasm of most women for the value of early detection.
RC: ▪ Not a systematic review, but a narrative review ▪ Author reports on 24 studies addressing psychological effects of screening and found some evidence of anxiety prior to mammography but no evidence of clinically meaningful depression or distress. ▪ No mention is made as to whether any of the studies were critically appraised

Fischer 04

Topic: MRI High Risk Women Preop

Reference: Fischer U, Zachariae O, Baum F, et al: The influence of preoperative MRI of the breasts on recurrence rate in patients with breast cancer. EurRadiol 14:1725-1731, 2004.

Delfini Grade: U

AHRQ Grade: High risk of bias

There is sufficient uncertainty that caution is urged regarding its use in making health care decisions.

Abstract

Preoperative MRI of the breasts has been proven to be the most sensitive imaging modality in the detection of multifocal or multicentric tumor manifestations as well as simultaneous contralateral breast cancer. The aim of the presented retrospective study was to evaluate the benefit of preoperative MRI for patients with breast cancer. Preoperative MRI performed in 121 patients (group A) were compared to 225 patients without preoperative MRI (group B). Patients of group A underwent contrast-enhanced MR imaging of the breast using a 2D FLASH sequence technique (TR/TE/FA 336 ms/5 ms/90°; 32 slices of 4-mm thickness, time of acquisition 1:27 min, contrast agent dosage 0.1 mmol Gd-DTPA/kg bw). All patients had histologically verified breast cancer and follow-up for more than 20 months (mean time group A: 40.3 months, group B: 41 months). Both groups received the same types of systemic treatment after breast conserving surgery. The in-breast tumor recurrence rate in group A was 1/86 (1.2%) compared to 9/133 (6.8%) in group B. Contralateral carcinoma were detected within follow-up in 2/121 (1.7%) in group A vs. 9/225 (4%) in group B. All results were statistically significant (P<0.001). Based on these results, preoperative MRI of the breasts is recommended in patients with histopathologically verified breast cancer for local staging.

Reviewer Comment:

- Subject to selection and other bias because not RCT.

Study Type

- Retrospective, single-center, cohort study.

Funding Source

Details: No mention

Aim

Details	Investigation of whether there is a positive influence of preoperative local MRI staging on patients with breast cancer considering the rate of ipsilateral tumor recurrence or metachronous contralateral carcinoma.

Outcome Measures

Details	Primary Outcome(s) ▪ In-breast recurrence rates; contralateral breast detection rates.

Population Inclusions Exclusions and Interventions

Details	**Inclusion criteria:** – Age of the patient: >18 years and <78 years – Primary diagnosis of breast carcinoma – Interval between imaging and surgery <4 weeks – Histopathologically verified R0 resection with tumor-free sections 1mm – Standardized surgical approach – Standardized adjuvant irradiation therapy after breast conserving therapy and adjuvant systemic therapy (hormonal-/chemotherapy) as recommended by international or national standards – Standardized follow-up >20 months

	Exclusion criteria: – Hematogeneous metastases of the breast carcinoma – Other concomitant malignant diseases

Diagnostic Issues

Threats	• Retrospective design: selection bias possible • No blinding • Not consecutive patients • No adjustment for differences in for differences in tumor size, nodal status, and the use of systemic therapy between the groups. • MR imaging of both breasts was performed in a 1.5-T whole-body system Magnetom SP 63 (Siemens Company, Erlangen, Germany) using a bilateral breast surface coil. Dynamic MRI measurements were performed repetitively before and five times after i.v. administration of 0.1 mmol gadopentetate-dimeglumine (Gd-DTPA, Magnevist, Schering Germany, Berlin) per kilogram bodyweight. • All pts. with histological dx and 20 month follow-up.

Selected Authors' Conclusions:

Based on these results, preoperative MRI of the breasts is recommended in patients with histopathologically verified breast cancer for local staging.

Hoshaw 01

Reference	Abstract	Comments
Hoshaw SJ, Klein PJ, Clark BD, Cook RR, Perkins LL. Breast implants and cancer: causation, delayed detection, and survival. Plast Reconstr Surg. 2001 May;107(6):1393-407. PubMed PMID: 11335807.	Concern for many women with breast implants has been focused on three topics: cancer (both breast and other cancers), delayed detection of breast cancer, and increased breast cancer recurrence or decreased length of survival. In this study, a qualitative review of the literature on these subjects was conducted, coupled with a metaanalysis of the risk for breast cancer or other cancers (excluding that of the breast). Researchers have consistently found no persuasive evidence of a causal association between breast implants and any type of cancer. The metaanalysis results obtained by combining the epidemiology studies support the overall conclusion that breast implants do not pose any additional risk for breast cancer (relative risk, 0.72; 95% confidence interval, 0.61 to 0.85) or for other cancers (relative risk, 1.03; 95% confidence interval, 0.87 to 1.24). This analysis suggests that breast implants may confer a protective effect against breast cancer. Women with implants should be reassured by the consistency of scientific studies which have uniformly determined that, compared with women without implants, they are not at increased risk for cancer, are not diagnosed with later-stage breast malignancies, are not at increased risk for breast cancer recurrence, and do not have a decreased length of survival.	Qualitative Safety Review Delfini evidence grade: Grade U AHRQ Rating of Bias: High

Houssami 08

Study Reference: Houssami N, Ciatto S, Macaskill P, Lord SJ, Warren RM, Dixon JM, Irwig L. Accuracy and surgical impact of magnetic resonance imaging in breast cancer staging: systematic review and meta-analysis in detection of multifocal and multicentric cancer. J Clin Oncol. 2008 Jul 1;26(19):3248-58. Epub 2008 May 12. Review. PubMed PMID: 18474876.

Purpose

We review the evidence on magnetic resonance imaging (MRI) in staging the affected breast to determine its accuracy and impact on treatment.

Methods

Systematic review and meta-analysis of the accuracy of MRI in detection of multifocal (MF) and/or multicentric (MC) cancer not identified on conventional imaging. We estimated summary receiver operating characteristic curves, positive predictive value (PPV), true-positive (TP) to false positive (FP) ratio, and examined their variability according to quality criteria. Pooled estimates of the proportion of women whose surgery was altered were calculated.

Results

Data from 19 studies showed MRI detects additional disease in 16% of women with breast cancer (N = 2,610). MRI incremental accuracy differed according to the reference standard (RS; *P* = .016) decreasing from 99% to 86% as the quality of the RS increased. Summary PPV was 66% (95% CI, 52% to 77%) and TP:FP ratio was 1.91 (95% CI, 1.09 to 3.34). Conversion from wide local excision (WLE) to mastectomy was 8.1% (95% CI, 5.9 to 11.3), from WLE to more extensive surgery was 11.3% in MF/MC disease (95% CI, 6.8 to 18.3). Due to MRI-detected lesions (in women who did not have additional malignancy on histology) conversion from WLE to mastectomy was 1.1% (95% CI, 0.3 to 3.6) and from WLE to more extensive surgery was 5.5% (95% CI, 3.1 to 9.5).

Conclusion

MRI staging causes more extensive breast surgery in an important proportion of women by identifying additional cancer, however there is a need to reduce FP MRI detection. Randomized trials are needed to determine the clinical value of detecting additional disease which changes surgical treatment in women with apparently localized breast cancer.

Reviewer Evidence Rating:

Delfini Grade: BU

AHRQ Rating: Moderate Risk of Bias

Delfini Evidence Statement:

The evidence might be sufficient to use in making health care decisions; however, there remains sufficient uncertainty that the evidence cannot fully reach a Grade B and the uncertainty is not great enough to fully warrant a Grade U. Study quality is such that it appears likely that the evidence is sufficient to use in making health care decisions; however, there are some study issues that raise continued uncertainty. Health care decision-makers should be fully informed of the evidence quality.

Reviewer Comment:

- MRI in women with breast cancer undergoing staging is associated with changes in surgical treatment.

Study Type

Meta-analysis of studies reporting MRI in staging of breast cancer determine MRI accuracy and impact on treatment.

Funding Source

Supported in part by National Health and Medical Research Council program Grant No. 402764 to the Screening and Test Evaluation Program.

Aim

Details	To provide a systematic review and meta-analysis of the incremental accuracy and impact of breast MRI

	in the context of local staging, with a focus on detection of MF and MC disease (detection of otherwise occult foci that are distinct from the index cancer).
Definitions	MF: multifocal = several foci same quadrant MC: multicentric = foci in different quadrants

Population and N

Nineteen studies were eligible for inclusion in our analysis providing data for 2,610 women with breast cancer (from 2,763 cases). Prevalence of detection of additional foci (MF or MC) in the affected breast ranged from 6% to 34% across studies with a median of 16%(interquartile range, 11% to 24%).

Inclusion Criteria For Studies

	Eligibility was determined according to whether the study examined MRI detection or accuracy in local staging (or in determining disease extent) in women with proven or suspected breast cancer and provided a measure of MRI accuracy for the detection of additional tumor foci (MF or MC) other than the index cancer. For inclusion in the analysis, studies must have provided the following for the ipsilateral breast: data on MRI-detected foci that were not identified on baseline clinical and imaging assessment (otherwise occult malignancy) or data that allow reliable calculation of MRI-only detection; data for both true positive (TP) and false positive (FP) detection as a minimum measure of accuracy; data that could be reliably distinguished from those relating to the diagnosis or measurement of the index cancer. Criteria for quality appraisal were based on standards for studies of test accuracy.

::SECONDARY STUDY

Search Strategy

Details	MEDLINE (1966 to week 1 June 2007), studies identified in the literature search, and in reference lists from primary studies and reviews, and through discussion with content experts.
	▪ No remarks

Selection and Critical Appraisal Methods

	(N=35) studies were reviewed by one of the authors and studies not meeting eligibility criteria were excluded. All eligible primary studies (n = 26) were reviewed independently by two of four authors and the reasons for excluded studies. There were 10 prospective studies, seven retrospective studies and two studies did not report design and could not be classified.

Combining Results

	Detailed model

Heterogeneity for Meta-analyses

	Yes. Details not reported

Weighting

	▪ No

Sensitivity Analysis

	▪ Results reported by quality of reference standard (based on morphology and kinetics considerations)

Diagnostic Issues

	• Information was extracted on the technology used (available from the authors) but in brief all studies used a dedicated breast coil and contrast-enhanced MRI. Ten studies specified that

	kinetics and morphology were used for MRI interpretation, five studies used morphology only, and four studies did not sufficiently report on this issue. • Retrospective and prospective studies were included. • Quality was assessed with the following: were consecutive patients included? was the reference standard adequate and applied in all patients?
Threats	• No mention of blinding • No details regarding percent of patients not receiving reference standard • Loss of data but not quantified

Screening

Threat	Problems identified
Threat	▪ There is no evidence that early diagnosis and treatment will improve outcomes compared to later diagnosis and treatment

Blinding

	▪ No mention of blinding

Missing Values in Results

	Yes. Total missing not stated.

Meta-Analysis Results

- 13 studies that provided relevant information : the proportion of patients in whom MRI affects surgical treatment ranges between 7.8% and 33.3%.
- Meta-analysis of the proportion of women who were changed to more extensive surgery due to MRI, in studies that provided specific data on actual conversion of surgery, gave the following summary estimates in women who had histology-proven additional foci of cancer detected by MRI: conversion from WLE to mastectomy was 8.1% (95% CI, 5.9 to 11.3) and conversion from WLE to more extensive surgery (wider/additional excisionor mastectomy) was 11.3% (95% CI, 6.8 to 18.3).
- Summary estimates in women who had additional lesions detected by MRI and in whom histology did not identify any additional malignancy (ie, change in surgery due to FP detection): conversion from WLE to mastectomy was 1.1% (95% CI, 0.3 to 3.6) and conversion from WLE to more extensive surgery (wider/additional excision or mastectomy) was 5.5% (95% CI, 3.1 to 9.5).

Kuhl 10

MRI, US, Mammography in High Risk Women

Kuhl C, Weigel S, Schrading S, Arand B, Bieling H, König R, Tombach B, Leutner C, Rieber-Brambs A, Nordhoff D, Heindel W, Reiser M, Schild HH. Prospective multicenter cohort study to refine management recommendations for women at elevated familial risk of breast cancer: the EVA trial. J Clin Oncol. 2010 Mar 20;28(9):1450-7. Epub 2010 Feb 22. PubMed PMID: 20177

Abstract

We investigated the respective contribution (in terms of cancer yield and stage at diagnosis) of clinical breast examination (CBE), mammography, ultrasound, and quality-assured breast magnetic resonance imaging (MRI), used alone or in different combination, for screening women at elevated risk for breast cancer.

Methods

Prospective multicenter observational cohort study. Six hundred eighty-seven asymptomatic women at elevated familial risk (≥20% lifetime) underwent 1,679 annual screening rounds consisting of CBE, mammography, ultrasound, and MRI, read independently and in different combinations. In a subgroup of 371 women, additional half-yearly ultrasound and CBE was performed more than 869 screening rounds. Mean and median follow-up was 29.18 and 29.09 months.

Results

Twenty-seven women were diagnosed with breast cancer: 11 ductal carcinoma in situ (41%) and 16 invasive cancers (59%). Three (11%) of 27 were node positive. All cancers were detected during annual screening; no interval cancer occurred; no cancer was identified during half-yearly ultrasound. The cancer yield of ultrasound (6.0 of 1,000) and mammography (5.4 of 1,000) was equivalent; it increased nonsignificantly (7.7 of 1,000) if both methods were combined. Cancer yield achieved by MRI alone (14.9 of 1,000) was significantly higher; it was not significantly improved by adding mammography (MRI plus mammography: 16.0 of 1,000) and did not change by adding ultrasound (MRI plus ultrasound: 14.9 of 1,000). Positive predictive value was 39% for mammography, 36% for ultrasound, and 48% for MRI.

Conclusion

In women at elevated familial risk, quality-assured MRI screening shifts the distribution of screen-detected breast cancers toward the preinvasive stage. In women undergoing quality assured MRI annually, neither mammography, nor annual or half-yearly ultrasound or CBE will add to the cancer yield achieved by MRI alone.

Reviewer Grade

Delfini grade: BU

AHRQ rating: Medium risk of bias

The evidence might be sufficient to use in making health care decisions; however, there remains sufficient uncertainty that the evidence cannot fully reach a Grade B and the uncertainty is not great enough to fully warrant a Grade U. Study quality is such that it appears likely that the evidence is sufficient to use in making health care decisions; however, there are some study issues that raise continued uncertainty. Health care decision-makers should be fully informed of the evidence quality.

Reviewer Comment:

- Aim was to assess cancer yield and stage at diagnosis of CBE, mammography, ultrasound, and breast MRI, used alone and in different combinations, for screening of women at elevated risk for breast cancer quantified using the BRCAPRO model and the cancer yield of additional half-yearly screening with ultrasound and CBE in a subgroup of 371 women.
- Overall detection rate was 15.5 per 1,000 woman-years
- All women were diagnosed with the combination of MRI and mammography.
- Based on BIRADS (Breast Imaging Reporting And Data System) score of 4 or 5 as a positive result, only two tumors were missed by MRI, but these were detected by mammography.
- MRI sensitivity (92.6%) and positive predictive value (PPV, 48%) were highest.

- Ultrasound added slightly to the efficacy of mammography, but not to that of MRI. The cancer yield of ultrasound (6.0 of 1,000) and mammography (5.4 of 1,000) was equivalent; it increased nonsignificantly (7.7 of 1,000) if both methods were combined.
- The high diagnostic accuracy of MRI as shown by receiver operating characteristic (ROC) analysis was not significantly improved by the addition of one or any combination of the other screening modalities.
- Authors consider discontinuing mammographic screening in young women who have access to quality-assured screening breast MRI possibly reasonable at this time and certainly if further studies confirm the high sensitivity of MRI for both invasive breast cancers and for DCIS as shown in the EVA trial.

Study Type

- Prospective multicenter observational cohort diagnostic study.

Funding Source

Details: Supported by Grant No. 70-2944 from the German Cancer Aid Society.

Aim / Objectives

Details	To prospectively – using a screening study methodology report the respective cancer yield and diagnostic accuracy of the different breast imaging methods (mammography, MRI, and ultrasound, used alone or in different combinations) for screening women at elevated familial risk. Secondary objective was to investigate the cancer yield of additional half-yearly screening with ultrasound and clinical breast examination (CBE).

Definitions Inclusions Exclusions

Details	Required to meet one of the following for inclusion: Two or more first-degree relatives with breast and/or ovarian cancer, at least one of whom received a diagnosis before age 50 years; A single first-degree relative with breast cancer diagnosed before age 35 years; A single first-degree relative with ovarian cancer diagnosed before age 40 years; A single male first-degree relative with breast cancer; A single first-degree relative with bilateral primary breast cancer diagnosed before age 50 years; A single first-degree relative with both, breast and ovarian cancer; Two or more first-degree relatives with breast cancer diagnosed before age 50 years; Three or more first- or second-degree relatives with breast cancer at any age; Documented mutation in a breast cancer–relevant gene; Women with a personal history of breast cancer were included as long as they had not undergone bilateral mastectomy, had not received chemotherapy during the last 12 months, and had not been diagnosed with distant metastases.
N	Eligible: 725; 38 lost to f/u; **687 women analyzed** (total of 1,741 annual screening rounds); 62 incomplete imaging; 1679 in accuracy calculations;
Population	• Women with familial history of breast cancer, no documented mutation: 63.5% • Women with familial and personal history of breast cancer, no documented mutation: 27% • Documented BRCA mutation (some with history of breast cancer): 9.5% (BRCA2 1.7%)
Threats	Some loss

Diagnostic Issues

Area	• BIRADS diagnoses of all recorded lesions were dichotomized in that categories 1, 2, and 3 were taken as test negative, and 4 and 5 were taken as test positive result. • Histopathologic diagnoses were dichotomized in that a diagnosis of invasive or DCIS cancer was accepted as a malignant diagnosis or disease positive; all other histologic results including

	lobular carcinoma in situ were categorized as benign or disease negative. An uneventful follow-up at 12 months was accepted as disease negative. • Images were read independently in different combinations and completed within 6 week period. Suggestive of adequate assessor blinding to other diagnostic tests. • Time between assessments reasonable • Mean f/u was 29 months • Statistics were reported
	•

Selected Authors' Conclusions:
In close agreement with the recently published American College of Radiology Imaging Network 6666 study, adding ultrasound to mammography increased the cancer yield by almost 50%. However, the direct comparison with MRI in the same patients reveals that even if ultrasound is added to mammography, only about half of the breast cancers are detected. Accordingly, ultrasound appears to be complementary to mammography, but not to MRI, and is no equivalent replacement for MRI.

If further studies confirm the high sensitivity of MRI for invasive cancers and for DCIS that was found in the EVA trial, then it is conceivable to discontinue mammographic screening in young women who have access to quality assured screening breast MRI. Even existing evidence suggests that this may be an option for (or may even be advisable to) young women under 40, especially if they carry a *BRCA1* mutation or a high risk of heterozygosity. In these women, mammographic sensitivity is known to be exceedingly low. This is not only caused by the very early onset of breast cancer and the on average dense breast tissue of these women, but also by the specific mammographic features of *BRCA1*-associated cancers. These cancers lack mammographically detectable calcifications, and if at all visible, they exhibit benign mammographic features. Therefore, the diagnostic benefit attributable to mammographic screening will be low. In contrast, the radiation dose will not be negligible if—per current guidelines—annual bilateral two view screening mammography is started at age 25 to 30 years. This dose will be imposed on young fibroglandular tissue that is more susceptible to the mutagenic effects of radiation. In addition, there is the still unsettled issue of an increased radiation sensitivity of *BRCA1* mutation carriers. The risk/benefit ratio of mammographic screening has been established only for women older than 40 years of age (many radiation biologists would argue only for women older than age 49 years). The guidelines for screening women with familial clustering of breast cancer, however, were released without prior radiobiologic modeling to estimate the risks associated with such recommendations, and none of the existing radiobiologic models would at all account for the availability of equivalent or superior diagnostic methods not associated with ionizing radiation. Current guidelines will subject high-risk women to a substantially higher lifetime glandular dose, imposed on less radiation-tolerant fibroglandular tissue, for a predictably substantially lower diagnostic benefit compared with regular mammographic screening. Therefore, although the number o mutation carriers was low in the EVA trial, existing evidence (or lack thereof) should call for a careful reappraisal of surveillance guidelines for high-risk women younger than age 40years, especially those with *BRCA1*mutation.

RESULTS

- Twenty-seven women (27 of 687; 3.9%) were diagnosed with breast cancer.
- **MRI missed two cancers (two of 27; 7%) in two women.**
- Annual breast cancer incidence was 15.5% (27 of 1,741), with 13.9% (10 of 718) in the first, 16.2% (10 of 617) in the second and 17.2% (seven of 406) in the third year.
- All cancers were diagnosed during the annual screening rounds.
- The sensitivity achieved by ultrasound alone (37%) and mammography alone (33%) was comparable (P<.72);
- The combined use of mammography and ultrasound yielded a statistically not significantly higher sensitivity (48%;P=.12).
- MRI alone was significantly more sensitive (93%) than mammography or ultrasound alone (P < .0001) or combined (P < .005). Adding mammography to MRI did not allow a statistically significant increase of sensitivity (P=.5).
- The positive predictive value was highest for MRI (48.0%), followed by mammography (39.1%) and ultrasound (35.7%).
- Clinical examination was positive in 110 screening rounds. In one of these, the palpable abnormality corresponded to breast cancer. All other cancers were clinically occult at the time of diagnosis. In the

remaining 109 palpable findings, a final diagnosis of benign changes was established either by biopsy or by an uneventful follow-up. The sensitivity was 3% (one of 27) and a positive predictive value of 0.9% (one of 110) for CBE.

- In summary, two cancers were only diagnosed by mammography (two of 27, 7%), none was only diagnosed by ultrasound, and 14 cancers (14 of 27, 52%) were only diagnosed by MRI; these were eight (50%) of the total 16 invasive cancers and six (55%) of the 11 DCIS. Thirty women (30 of 687; 4.4%) underwent biopsy for false positive diagnoses.

Lee 10
Economic Analysis
Citation: Lee JM, McMahon PM, Kong CY, Kopans DB, Ryan PD, Ozanne EM, Halpern EF, Gazelle GS. Cost-effectiveness of breast MR imaging and screen-film mammography for screening BRCA1 gene mutation carriers. Radiology. 2010 Mar;254(3):793-800. PubMed PMID: 20177093; PubMed Central PMCID: PMC2826703.
Manufacture Involvement: No
Reviewer Grade
Delfini Grade for Cost-effectiveness: U
AHRQ Grade for Cost-effectiveness: High risk of bias

Delfini Evidence Statement:

There is sufficient uncertainty that caution is urged regarding its use in making health care decisions.

PUBLISHED ABSTRACT SECTIONS (WHITE) WITH REVIEWER COMMENTS & KEY POINTS OF STUDY (RC IN GREY) [References removed]

Purpose: To evaluate the clinical effectiveness and cost-effectiveness of screening strategies in which MR imaging and screen-film mammography were used, alone and in combination, in women with BRCA1 mutations.

RC:
- U.S.-based analysis
- Modeled analysis
- Perspective = societal
- Lifetime costs were measured in 2007 dollars with an annual discount rate of 3%

Materials and Methods: Because this study did not involve primary data collection from individual patients, institutional review board approval was not needed. By using a simulation model, we compared three annual screening strategies for a cohort of 25-year-old BRCA1 mutation carriers, as follows: (a) screen-film mammography, (b) MR imaging, and (c) combined MR imaging and screen-film mammography (combined screening). The model was used to estimate quality-adjusted life-years (QALYs) and lifetime costs. Incremental cost-effectiveness ratios were calculated. Input parameters were obtained from the medical literature, existing databases, and calibration. Costs (2007 U.S. dollars) and quality-of-life adjustments were derived from Medicare reimbursement rates and the medical literature. Sensitivity analysis was performed to evaluate the effect of uncertainty in parameter estimates on model results.

RC:
- It was assumed that both tests were performed at the same time
- Diagnosis of cancer consisted of screening, diagnostic work-up and biopsy
    - Positive screening = additional mammographic views, with or without ultrasonography, following positive results resulting in biopsy
    - If a cancer was missed, cancer progression was assumed to continue until next screening or until it was clinically manifest as an interval cancer
- Input parameters included Leach 05 for measures of test function plus tumor size and invasiveness, Breast Cancer Surveillance Consortium (BCSC), Surveillance Epidemiology and End Results (SEER) Program. Public-use data, 1973-2001, National Cancer Institute, and Centers for Medicare and Medicaid Services (CMS) for cost data. Additional costs of care, patient time costs and quality-of-life (QOL) weights were derived from the medical literature.
- In the base case, no short-term QOL changes were made related to screening or false-positives; however, QOL weights were applied to women diagnosed in the model with breast cancer for five years after which they reverted to that of a same-age health cancer-free woman.

Results: In the base-case analysis, annual combined screening was most effective (44.62 QALYs), and had the highest cost ($110973), followed by annual MR imaging alone (44.50 QALYs, $108641), and annual mammography alone (44.46 QALYs, $100336). Adding annual MR imaging to annual mammographic screening cost $69125 for each additional QALY gained. Sensitivity analysis indicated that, when the screening MR imaging cost increased to $960 (base case, $577), or breast cancer risk by age 70 years decreased below 58% (base case, 65%), or the sensitivity of combined screening decreased below 76% (base case, 94%), the cost of adding MR imaging to mammography exceeded $100000 per QALY.

RC:

- Sensitivity analyses were performed including to evaluate—
    - Diagnostic test performance testing Leach 09 statistics with others reported in the literature
    - Potential effect of risk-reducing prophylactic oophorectomy wherein the risk of breast cancer was reduced by 50%, following prophylactic oophorectomy at ages 35, 40, or 45 years.
        - Mortality risk from ovarian cancer was subsequently subtracted
- Short-term QOL effects were included in sensitivity analyses
- Dependencies included strong dependence upon MRI imaging cost and underlying breast cancer risk
- In this analysis, MRI was reported as being—
    - More cost-effective under the following conditions—
        - Breast cancer risk increases
    - Less cost-effective under the following conditions—
        - Breast cancer risk decreases
- Cost effectiveness was also influenced by measures of test function
- Additional sensitivity analyses of costs, annual discount rate, quality-of life weights, and natural history parameter values were performed, all of which yielded ICER values less than $100 000 per QALY

Conclusion: Annual combined screening provides the greatest life expectancy and is likely cost-effective when the value placed on gaining an additional QALY is in the range of $50000-$100000.

RC:

- Threshold cited was a range from $50,000 to $100,000 per QALY.

Lehman 07

MRI High Risk Women

Lehman CD, Isaacs C, Schnall MD, Pisano ED, Ascher SM, Weatherall PT, Bluemke DA, Bowen DJ, Marcom PK, Armstrong DK, Domchek SM, Tomlinson G, Skates SJ, Gatsonis C. Cancer yield of mammography, MR, and US in high-risk women: prospective multi-institution breast cancer screening study. Radiology. 2007 Aug;244(2):381-8. PubMed PMID: 17641362.

Abstract

Cancer yield of mammography, MR, and US in high-risk women: prospective multi-institution breast cancer screening study.

Lehman CD, Isaacs C, Schnall MD, Pisano ED, Ascher SM, Weatherall PT, Bluemke DA, Bowen DJ, Marcom PK, Armstrong DK, Domchek SM, Tomlinson G, Skates SJ, Gatsonis C.

Abstract

PURPOSE:
To prospectively determine cancer yield, callback and biopsy rates, and positive predictive value (PPV) of mammography, magnetic resonance (MR) imaging, and ultrasonography (US) in women at high risk for breast cancer.

MATERIALS AND METHODS
The study was approved by the institutional review board and was HIPAA compliant, and informed consent was obtained. We conducted a prospective pilot study of screening mammography, MR, and US in asymptomatic women 25 years of age or older who were genetically at high risk, defined as BRCA1/BRCA2 carriers or with at least a 20% probability of carrying a BRCA1/BRCA2 mutation. All imaging modalities were performed within 90 days of each other. Data were analyzed by using exact confidence intervals (CIs) and the McNemar test.

RESULTS
A total of 195 women were enrolled in this study over a 6-month period, and 171 completed all study examinations (mammography, US, and MR). Average age of the 171 participants was 46 years +/- 10.2 (standard deviation). Sixteen biopsies were performed and six cancers were detected, for an overall 3.5% cancer yield. MR enabled detection of all six cancers; mammography, two; and US, one. The diagnostic yields for each test were 3.5% for MR, 0.6% for US, and 1.2% for mammography. MR, US, and mammography findings prompted biopsy in 8.2%, 2.3%, and 2.3% of patients, respectively. None of the pairwise comparisons were statistically significant. The PPV of biopsies performed as a result of MR was 43%. CONCLUSION: Screening MR imaging had a higher biopsy rate but helped detect more cancers than either mammography or US. US had the highest false-negative rate compared with mammography and MR, enabling detection of only one in six cancers in high-risk women.

PMID: 1764136

Reviewer Grade BU

AHRQ Risk of Bias Rating: Medium

Delfini Evidence Statement:

The evidence might be sufficient to use in making health care decisions; however, there remains sufficient uncertainty that the evidence cannot fully reach a Grade B and the uncertainty is not great enough to fully warrant a Grade U. Study quality is such that it appears likely that the evidence is sufficient to use in making health care decisions; however, there are some study issues that raise continued uncertainty. Health care decision-makers should be fully informed of the evidence quality.

Reviewer Comment:

- Screening MR allowed detection of more cancers (n = 6) in 171 high risk women (3.5%) compared with screening US (n = 1) and/or screening mammography (n =2).
- No additional information was provided by US.
- Annual screening with MR in high risk women may yield 23 cancers additional cancers per 1000 women screened with MR.
- The risk of false positives is this study was 5% (women undergoing biopsy resulting in a benign outcome).

- Consistent with other studies in high risk women demonstrating that MR has higher sensitivity in cancer detection than mammography at the cost of a higher biopsy rate.

Study Type

- Six center prospective cohort diagnostic study.

Funding Source

Details: Supported by the International Breast MRI Consortium (grants U01 CA74680 and 5 U01 CA74696) and the Cancer Genetics Network (grant U24 CA78146-01).

Aim

Details	To prospectively determine cancer yield, callback and biopsy rates, and positive predictive value (PPV) of mammography, magnetic resonance (MR) imaging, and ultrasonography (US) in women at high risk for breast cancer.

Outcome Measures

Details	Primary Outcome(s) ▪ Primary interest was the diagnostic performance of MR imaging in high risk women

Definitions Inclusions Exclusions

Details	A woman was determined to be high risk if she met any of the following criteria: 1. Tested positive for *BRCA1/ BRCA2* mutation or had a first- or second-degree relative who tested positive for either mutation; 2. The probability of carrying a *BRCA1/BRCA2* mutation (given family history of breast and ovarian cancer) was found to exceed 20%, as determined with BRCAPRO; 3. The family contained at least two instances of ovarian or breast cancer among the participant and first- or second- degree relatives within the same lineage (multiple primary cancers within same person met criteria); or 4. The woman was of Ashkenazi Jewish ethnicity with one first- or two second-degree relatives with breast or ovarian cancer or was Ashkenazi Jewish and had breast cancer. Where breast cancer was required to meet criteria, participant age of diagnosis of at least one of the breast cancers must have been premenopausal or less than 50 years old. Women were excluded on the basis of the following criteria: 1. Known contraindication to MR: pregnancy, pacemaker, magnetic aneurysm clip or other implanted magnetic device, or severe claustrophobia; 2. Current palpable or mammographic- actionable finding known at time of enrollment assessment (benign findings at mammography or physical examination allowed); 3. Prior biopsy in the study breast within the past 6 months (including fine needle aspiration); 4. Received adjuvant chemotherapy or radiation therapy within 6 months of study entry (may have been receiving tamoxifen or aromatase inhibitor either as adjuvant hormonal therapy or for preventive measures); 5. A first- or second-degree relative with a *BRCA1/BRCA2* mutation and the potential participant tested negative for the same mutation; 6. Current untreated malignancy (other than nonmelanoma skin cancer); 7. Metastatic malignancy within the past 5 years; and 8. A psychiatric condition preventing fully informed consent.
N	Eligible: 190; 19 did not have imaging; 171 with mammograms, MRI, US; 144 did not have positive results; 60 positive findings
Threats	Some loss; relatively small study

Diagnostic Issues

Area	• Separate readers to ensure blind assessment • Gold standard = biopsy applied to most • Time between assessments reasonable • Statistics were reported • 1.5-T magnet strength, a dedicated breast coil for MRI

Selected Authors' Conclusions:

In conclusion, our multi-institutional study further supports MR as an important complement to mammography in screening women at high risk for breast cancer. At this time, further studies are needed to more clearly address the potential role of US in this patient population before it can be promoted as a reasonable alternative to MR for screening women at high risk.

RESULTS

- N=171/195 completed MR, mammography, US
- 16 biopsies
- **6 cancers (3.5%)**

- **MR: 6 detected with MR (3.5% detection rate); MR prompted biopsy in 8.2% of patients. Approx. 5% false positives for MR; PPV for MR was 43%**

- Mammography: 2 detected with mammography (1.2% detection rate); prompted biopsy in 2.3%
- US: 1 detected with US (0.6% detection rate); prompted biopsy in 2.3%

Lim 10
MRI and Changes in Operative Management
Citation: Lim HI, Choi JH, Yang JH, Han BK, Lee JE, Lee SK, Kim WW, Kim S, Kim JS, Kim JH, Choe JH, Cho EY, Kang SS, Shin JH, Ko EY, Kim SW, Nam SJ. Does pre-operative breast magnetic resonance imaging in addition to mammography and breast ultrasonography change the operative management of breast carcinoma? Breast Cancer Res Treat. 2010 Jan;119(1):163-7. PubMed PMID: 19760039.
Manufacture Involvement: Uncertain
Delfini Grade: BU for change in treatment plans
AHRQ Risk of Bias Rating: Medium

PUBLISHED ABSTRACT SECTIONS WITH REVIEWER COMMENTS (RC)

Magnetic resonance imaging (MRI) has been used for the local staging of breast cancer, especially to determine the extent of multiple lesions and to identify occult malignancies. The aim of this study was to evaluate the effect of pre-operative MRI on the surgical treatment of breast cancer.

Between January 2006 and May 2007, 535 newly diagnosed breast cancer patients who planned to undergo breast conserving surgery had clinical examinations, bilateral mammography, breast ultrasonography, and breast MRI. The radiologic findings and clinicopathologic data were reviewed retrospectively.

Ninety-eight (18.3%) patients had additional lesions, shown as suspicious lesions on breast MRI, but not detected with conventional methods. Eighty-four (15.7%) of these patients had a change in surgical treatment plans based on the MRI results. Forty-seven (8.8%) of the 84 patients had additional malignancies; the other 37 patients (6.9%) had benign lesions. The positive predictive value for MRI-based surgery was 56.0% (47 of 84 patients). During the period of study, the use of pre-operative MRI was increased with time (OR 1.20; 95% CI 1.16-1.23; P < 0.001), but the mastectomy rate did not change significantly (OR 0.98; 95% CI 0.95-1.00; P = 0.059). Multiple factors were analyzed to identify the patients more likely to undergo appropriate and complete surgery based on the additional findings of the pre-operative MRI, but the results were not statistically significant.

This research suggests that a pre-operative MRI can potentially lower the rate of incompletely excised malignancies by identifying additional occult cancer prior to surgery and does not lead to an increase in the mastectomy rate; however, because some benign lesions are indistinguishable from suspicious or malignant lesions, excessive surgical procedures are unnecessarily performed in a significant portion of patients. In the future, the criteria for the use of MRI in local staging of breast cancer should be established.

RC: Reliable scientific conclusions cannot be drawn from this study.

- Single center study performed in Korea.
- Results are reported by the authors as "suggestive."
- The authors state the following—
    - This study focused on the ability of MRI to find additional lesions, but the outcomes after treatment were not considered. Therefore, we could not conclude that preoperative MRI affords patients newly diagnosed with breast cancer a better prognosis.
    - However, this research suggests that pre-operative MRI could potentially lower the rate of incompletely excised malignancies and some patients might be saved from the risk of loco-regional treatment failure by the appropriate and complete surgery based on pre-operative MRI results.
    - Because the period of follow-up was not >3 years, it was not sufficient to achieve reliable results. Thus, the results of this study cannot be extended to all breast cancers.
    - Although in this study, we could not determine the factors which were associated with the patients who were saved from an incomplete surgery, the efforts will continue to establish criteria for the use of preoperative breast MRI based on the results that pre-operative breast MRI helped to facilitate a complete surgery for some patients.

Lord 07

Study Reference: Lord SJ, Lei W, Craft P, Cawson JN, Morris I, Walleser S, Griffiths A, Parker S, Houssami N. A systematic review of the effectiveness of magnetic resonance imaging (MRI) as an addition to mammography and ultrasound in screening young women at high risk of breast cancer. Eur J Cancer. 2007 Sep;43(13):1905-17. Epub 2007 Aug 2. Review. PubMed PMID: 17681781

Abstract

Breast magnetic resonance imaging (MRI) has been proposed as an additional screening test for young women at high risk of breast cancer in whom mammography alone has poor sensitivity. Investigators conducted a systematic review to assess the effectiveness of adding MRI to mammography with or without breast ultrasound and clinical breast examination (CBE) in screening this population. They found consistent evidence in 5 studies that adding MRI provides a highly sensitive screening strategy **(sensitivity range: 93-100%) compared to mammography alone (25-59%) or mammography plus ultrasound+/-CBE (49-67%).**

Meta-analysis of the three studies that **compared MRI plus mammography versus mammography alone showed the sensitivity of MRI plus mammography as 94% (95%CI 86-98%) and the incremental sensitivity of MRI as 58% (95%CI 47-70%).** Incremental sensitivity of MRI was lower when added to mammography plus ultrasound (44%, 95%CI 27-61%) or to the combination of mammography, ultrasound plus CBE (31-33%).

Estimates of screening specificity with MRI were not consistent but suggested **a 3-5-fold higher risk of patient recall for investigation of false positive results. Based on 2 of the included studies, the risk for undergoing a percutaneous biopsy without finding cancer was approximately 3-fold higher. One study suggested that the risk of undergoing a surgical biopsy with benign findings was approximately doubled.**

No studies assessed as to whether adding MRI reduces patient mortality, interval or advanced breast cancer rates, and we did not find strong evidence that MRI leads to the detection of earlier stage disease.

Conclusions about the effectiveness of MRI in young women at high risk of breast cancer therefore depend on assumptions about the benefits of early detection based or reported results from trials of mammographic screening in older average risk populations. The extent to which high risk younger women receive the same benefits from early detection and treatment of MRI-detected cancers has not yet been established.

Reviewer Evidence Rating for Accuracy:

Delfini Grade: BU

AHRQ Rating: Medium Risk of Bias

Delfini Evidence Statement:

The evidence might be sufficient to use in making health care decisions; however, there remains sufficient uncertainty that the evidence cannot fully reach a Grade B and the uncertainty is not great enough to fully warrant a Grade U. Study quality is such that it appears likely that the evidence is sufficient to use in making health care decisions; however, there are some study issues that raise continued uncertainty. Health care decision-makers should be fully informed of the evidence quality.

Reviewer Comment: This meta-analysis was based on the best-available evidence using moderately strong methods for assessing studies for inclusion. Mammography, ultrasound and MRI each detected cancers that were not detected by the other modalities indicating that the use of all three tests in combination increases case finding. The addition of MRI to conventional screening increased detection by 8 to 24 additional breast cancers per 1000 screenings. Clinical outcomes, costs, adverse effects of MRI screening in this population were not addressed.

Note: The effectiveness of a screening test is demonstrated by showing that it reduces patient mortality. If there is evidence that it detects an increased number of cases of disease with a reduction in rates of interval cancers or the incidence of advanced cancers in subsequent screening rounds it may be reasonable to conclude that the evidence is suggestive of efficacy. We found no studies assessing the impact of MRI screening on any of these outcomes. Therefore conclusions about the efficacy of MRI as a screening test in women with increased risk of breast cancer (in this meta-analysis defined as young women with BRCA1 or BRCA2 or previous breast cancer) must based on evidence of improved sensitivity together with assumptions about the benefits of early detection, considering previous

evidence from studies of mammographic screening trials conducted in average risk populations who differ and whose breast cancers may differ significantly from women at higher risk. For example women in trials of average risk populations may be older and have different known and unknown prognostic variables. Breast cancers in younger high risk women may behave differently from those at average risk. The evidence is sufficient to conclude that the addition of MRI or MRI plus US results in the increased detection of breast cancer cases and that the evidence is insufficient to conclude that mortality or morbidity is decreased.

Young women at high risk for breast cancer should be thoroughly informed about the evidence for increased detection of breast cancer (increased detection of 1 to 3 breast cancers per 100 women screened) and the uncertainty about meaningful clinical benefit derived from the addition of MRI to mammography or mammography plus ultrasound in the screening for breast cancer. They should also be thoroughly informed about the possibility of false positive tests and the increased risk for further interventions such as recall for repeat testing, biopsy and other surgical interventions. Based on 2 of the included studies the risk for undergoing a percutaneous biopsy without finding cancer is approximately tripled. One study suggested that the risk of undergoing a surgical biopsy with benign findings is approximately doubled.

Recommendations for future research: Ideally valid RCTs reporting mortality outcomes would be performed in high-risk women. If such studies are not feasible because of size, length of required trials, cost, ethical or other considerations, evidence from trials demonstrating a stage shift in the detection of earlier stage breast cancer and improved outcomes for early versus late stage disease might also suggest benefit from MRI screening in high-risk women.

Study Type

Meta-analysis of studies of MRI using histology as the reference standard for positive tests and a consensus of all tests as the minimum reference standard for negative tests using data tables.

Funding Source

Department of Health and Ageing, Commonwealth of Australia for the assessment of magnetic resonance imaging of the breast.

Aim

Details	No existing systematic reviews have specifically investigated the incremental value of MRI as an addition to conventional imaging with mammography and ultrasound in young high risk women. This is a systematic review of the incremental accuracy of breast MRI as an addition to annual mammography with or without breast ultrasound and clinical breast examination (CBE) in screening women under 50 years which provides pooled estimates of screening accuracy and attempted to evaluate evidence relating to early detection and outcomes in this population. The review appraised evidence published up to March 2007 to assess the incremental accuracy of MRI, and compare prognostic characteristics of cancers detected by the addition of MRI versus those detected by conventional testing alone.

Outcome Measures

Details	incremental sensitivity and specificity of MRI as an additional test to the combination of mammography, ultrasound and CBE and/or mammography alone.

Population

Population: Mean/median age ranged from 40 to 47 years, although only one study restricted enrolment to women </=50 years. Risk criteria used to select subjects ranged from estimation of > /=20% cumulative lifetime risk to known BRCA1 or BRCA2 mutation carriers (estimated 65% cumulative lifetime risk). One study excluded participants with a prior history of breast cancer.

N: 4,534 MRI scans in 2059 women.

Inclusion Criteria For Studies

	Studies that compared the addition of MRI to mammography with or without ultrasound and CBE in asymptomatic high-risk women, and reported sufficient data for calculation of the incremental sensitivity (probability of a positive test in women with breast cancer) and specificity (probability of a negative test in

	women without breast cancer) of MRI using histology as the reference standard for positive tests and a consensus of all tests as the minimum reference standard for negative tests using data tables (see data analysis). Comparative studies reporting on prognostic tumor characteristics (tumor size and/or axillary lymph node involvement) of invasive cancers detected with the addition of MRI versus conventional imaging alone, interval cancer rates, or relevant patient outcomes were also eligible for inclusion.

::SECONDARY STUDY

Five accuracy studies were eligible for review. Four systematic reviews investigating MRI for breast cancer screening were identified: three were conducted prior to the publication of one or more eligible accuracy studies; the fourth included all eligible studies but did not specifically investigate the incremental value of MRI versus conventional imaging. The present systematic review appraises evidence published up to March 2007 to assess the incremental accuracy of MRI, and compare prognostic characteristics of cancers detected by the addition of MRI versus those detected by conventional testing alone.

Search Strategy

Details	Electronic databases (MEDLINE, Pre-Medline, EMBASE, the Cochrane Library) and websites of health technology assessment agencies were searched to identify relevant studies published in English between 1966 and March 2007 using Medical Subject Heading terms and text words for MRI and breast cancer.
	▪ No remarks

Critical Appraisal Methods

	Two independent reviewers assessed the quality of included studies using the QUADAS tool. Studies were classified as high quality if: they were conducted prospectively using well-defined selection criteria and recruited consecutive eligible subjects; reported on the execution of study tests and test threshold for a positive test in sufficient detail to allow test replication; applied the same reference standard to validate the results of study tests; interpreted test results without the knowledge of the reference standard or comparator tests; conducted study tests within two weeks; reported indeterminate test results; and explained study withdrawals. Studies not conducted prospectively or not meeting the criteria for an adequate reference standard or test interval were classified as low quality, other studies were classified as fair quality. Investigators also evaluated four previous reviews.

Combining Results

	Relative risk and absolute risk differences of false positive recall and benign biopsy rates (and 95%CI) were calculated.

Heterogeneity for Meta-analyses

	Heterogeneity between studies was assessed separately for estimates of sensitivity and specificity, and differences between tests in sensitivity and specificity, using Chi-squared tests. Heterogeneity between studies was assessed separately for estimates of sensitivity and specificity, and differences between tests in sensitivity and specificity, using Chi-squared tests. Metaanalysis of data from the three studies that compared the sensitivity and specificity of MRI plus mammography versus mammography alone - test for heterogeneity P = 0.84.

Weighting

	▪ No remarks

Sensitivity Analysis

	▪ Not done

Diagnostic Issues

	Studies were performed using MRI equipment with a field strength of 1.0–1.5 or 1.5 Tesla a dedicated breast coil and intravenous gadolinium contrast. **Statistical analysis** Two by two tables were reconstructed and per-patient sensitivity, specificity and associated 95% confidence intervals (CI) for test strategies with and without MRI were calculated using Meta-DiSc software. Differences in sensitivities and specificities between test strategies were calculated. Where appropriate, summary estimates and 95%CI of sensitivity and specificity for each test strategy, and the differences between strategies, were obtained using the random-effects method of DerSimonian-Laird.
Threats	• Different methods in studies for determining positive and inconclusive results. • Each study only reported data for the subset of eligible subjects who successfully received MRI and comparator tests. • Studies reported between 6% and 21% of enrolled subjects were subsequently excluded or lost to follow up.

Blinding

	▪ Outcome assessors were blinded to other tests

Missing Values in Results

Threat	Studies reported between 6% and 21% of enrolled subjects were subsequently excluded or lost to follow up.

Meta-Analysis Results

4 Previous Documents Review by Authors

- National Collaborating Centre for Primary Care. Familial breast cancer: The classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care. Partial update of NICE clinical guideline 14. <http://www.nice.org.uk/page.aspx?o=317667

- Saslow D, Boetes C, Burke W, et al. American cancer society guidelines for breast screening with MRI as an adjunct to mammography. CA: Cancer J Clin 2007;57:75–89.

- Irwig L, Houssami N, van Vliet C. New technologies in screening for breast cancer: a systematic review of their accuracy. Br J Cancer 2004;90:2118–22.

- National Breast Cancer Centre (NBCC). Magnetic resonance imaging for the early detection of breast cancer in women at high risk: a systematic review of the evidence. Camperdown: NBCC; 2006.

Flowchart Summarizing Search and Application of Relevance and Quality Criteria

Potentially relevant publications screened for retrieval (n = 3,309)

Retrieved (n=91) studies for full text for full-text evaluation after excluding ineligible studies because of design and methodological problems

Included in systematic review (n=5)

:: Table: Sensitivity / Specificity Breast Cancer Detection in High Risk Women (Lord 07 Meta-analysis)

Diagnostic Test	Sensitivity	Specificity
Mammography Alone	25% to 59%	NR
Mammography + US	49% to 67%	NR
Mammography + MRI versus Mammography Alone	94% (95% CI, 86 to 98); incremental sensitivity of MRI 58% (95% CI, 47 to 70%)	Specificity of MRI plus conventional testing varied across studies (range 77 to 96%) and precluded meta-analysis to estimate the "true" relative specificity of screening strategies versus without MRI.
MRI + Mammography + US	86% to 100%; incremental sensitivity of MRI 44%, (95% CI, 27 to 61%)	
MRI + Mammography + CBE	Incremental sensitivity of MRI 31%to 33%	

Relative Risk of Recall Rates: Further Investigation of False Positives And / Or Benign Percutaneous Biopsy (Core or Fine Needle) When MRI was added to mammography versus mammography alone	3.43 to 4.86
Estimated Additional False Positive Recalls Per 1000 Screening Rounds	71 to 74
Relative Risk of Undergoing Benign Percutaneous Biopsy Due to Addition of MRI to Mammography + US	1.22 to 9.50
Additional Benign Biopsies per 1000 Screening Rounds	7 to 46

Risk of Recall Rates: Further Investigation of False Positives And / Or Benign Percutaneous Biopsy (Core or Fine Needle) When MRI was added to mammography versus mammography alone

Relative Risk	risk 3.43–4.86
Estimated Additional False Positive Recalls Per 1000 Screening Rounds	71–74

Relative Risk of Undergoing A Benign Percutaneous Biopsy Due to Addition of MRI to Mammography + US

Relative Risk	1.22 to 9.50
Additional Benign Biopsies per 1000 Screening Rounds	7-46

:: Table: Results From 5 Included Studies (Lord 07)
NR = Not reported

Notes

- Number: Alphabetically arranged; reference number applies to the order in this table only (i.e., is not tied to **References**)

#	Author, Year, Population, Screening Strategy for Studies Included in Lord 07	Sensitivity (SN) and Specificity (SP) Without MRI	Sensitivity (SN) and Specificity (SP) With MRI	Incremental Cancer Yield and Test Sensitivity Using MRI	Relative Risk and Absolute Risk Difference (95% CI) of False Positive Patient Recall and Benign biopsies With and Without MRI
1.	Kuhl 2005 N=529 Median age 40 years; range 27 to 59 years) Prior history of breast cancer: 26% Conventional testing = mammography + ultrasound	SN 49% (33 to 65%) SP 89% (87 to 91%)	SN 93% (81 to 99%) SP NR	Incremental yield 19/1452; 13.1 additional cancers per 1000 screening rounds; Incremental SN 44% (27 to 61%)	False positive patient recall rate and benign biopsy rate NR
2.	Leach 2005 (magnetic resonance imaging breast screening (MARIBS)) United Kingdom 22 sites 1997–2004 N=649 Median age 40 years (range 31 to 55 years) Prior history of breast cancer: 0% Conventional testing = mammography	SN 40% (24 to 58%) SP 93% (92 to 95%)	SN 94% (81 to 99%) SP 77% (75 to 79%)	Incremental yield 19/1881; 10.1 additional cancers per 1000 screening rounds; Incremental SN 54% (36 to 72%)	False positive patient recall rate NR; Benign percutaneous biopsy rate: RR: 1.22 (0.83 to 1.80); RD: 7 (6 to 20) additional benign percutaneous biopsies per 1000 screening rounds

3.	Lehman 2005 (International Breast MRI Consortium Working Group (IBMC)) USA, Canada 13 sites 1999–2002 N=367 Mean age 45 years, standard deviation 9.7 years (range NR) Prior history of breast cancer: 10% Conventional testing = mammography	SN 25% (0.6 to 81%) SP 98% (96 to 99%)	SN 100% SP 91%	8.2 additional cancers per 1000 screening rounds; Incremental SN 75%	False positive patient recall: RR: 4.86 (2.18 to 10.82); RD: 74 (41 to 106) additional recalls per 1000 screening rounds; Benign percutaneous biopsy RR: 9.50 (2.23 to 40.49) RD: 46 (22 to 70) additional biopsies per 1000 screening rounds
4.	Sardanelli 2007 N=278 Mean age 46 years (range 25 to 79 years) Prior history of breast cancer: 39% Conventional testing = mammography + ultrasound + CBE	SN 67% (41 to 87%) SP NR	SN 100% (82 to 100%) SP 96% (94 to 98%)	15.9 additional cancers per 1000 screening rounds; Incremental SN 33% (11 to 55%)	False positive patient recall rate and benign biopsy rate NR
5.	Warner 2004 N=236 Median age: 47 years (range 25 to 65 years) Prior history of breast cancer: 30% Risk classification • BRCA1/2 mutation carriers 100% Conventional testing = mammography + ultrasound + CBE	1. Conventional testing = mammography + ultrasound + CBE: SN 64% (41 to 83%) SP NR 2. Conventional testing = mammography + CBE: SN 45% (24 to 68%) SP NR 3. Conventional testing=mammography: SN 36% (17 to 59%) SP 99.8% (99 to 100%)	1. Conventional testing = mammography + ultrasound + CBE: SN 95% (77 to 100%) SP NR 2. SN 86% (65 to 97%) SP NR 3. SN 86% (65 to 97%) SP NR	1. 15.3 additional cancers per 1000 screening rounds; Incremental SN 31% (10 to 54%) 2. 9.7 additional cancers per 1000 screening rounds 3. 24.1 additional cancers per 1000 screening rounds; Incremental SN 50% (25 to 75%)	1. False positive patient recall rate and benign biopsy rate NR 2. False positive patient recall rate and benign biopsy rate NR 3. False positive patient recall rate and benign biopsy rate NR

Investigators did not identify any studies that compared patient outcomes, reported mortality as an outcome or interval cancer rates in high risk women screened with and without MRI**.**

None of the studies reviewed compared rates of advanced cancers in successive screening rounds. There were no statistically significant differences in tumour size (<10mm or>/=20 mm) or lymph node involvement of invasive cancers detected with and without MRI.

Mann 10
MRI and Changes in Operative Management
Citation: Mann RM, Loo CE, Wobbes T, Bult P, Barentsz JO, Gilhuijs KG, Boetes C. The impact of preoperative breast MRI on the re-excision rate in invasive lobular carcinoma of the breast. Breast Cancer Res Treat. 2010 Jan;119(2):415-22. PubMed PMID: 19885731.
Manufacture Involvement: No disclosures
Reviewer Grades
Delfini Grade: BU to U
AHRQ Grade: High risk of bias

Delfini Evidence Statement:
The evidence might be sufficient to use in making health care decisions; however, the uncertainty is such that it might fully warrant a Grade U. Study is suggestive and requires confirmation through other studies that are of lower risk of bias.

PUBLISHED ABSTRACT SECTIONS WITH REVIEWER COMMENTS (RC)

Re-excision rates after breast conserving surgery (BCS) of invasive lobular carcinoma (ILC) are high. Preoperative breast MRI has the potential to reduce re-excision rates, but may lead to an increased rate of mastectomies. Hence, we assessed the influence of preoperative breast MRI on the re-excision rate and the rate of mastectomies.

We performed a retrospective cohort study of a consecutive series of patients with ILC who presented in one of two dedicated tertiary cancer centers between 1993 and 2005. We assessed the initial type of surgery (BCS or mastectomy), the re-excision rate and the final type of surgery. Patients were stratified into two groups: those who received preoperative MRI (MR+ group) and those who did not (MR- group).

In the MR- group, 27% of the patients underwent a re-excision after initial BCS. In the MR+ group, this rate was significantly lower at 9%.The odds ratio was 3.64 (95% CI: 1.30-10.20, P = 0.010).There was a trend towards a lower final mastectomy rate in the MR+ group compared to the MR- group (48 vs. 59%,P = 0.098).

In conclusion, preoperative MRI in patients with ILC can reduce re-excision rates without increasing the rate of mastectomies.

RC: Reliable scientific conclusions cannot be drawn from this study because of potential biases as summarized below. Selection and performance biases cannot be eliminated as reasons for the observed differences between groups because of the retrospective design. The study should be regarded as hypothesis-generating. Setting is tertiary dedicated cancer center which raises external validity issues as well.

- Observational retrospective study. Pathological and oncological databases were utilized.
- Wide time span from January 1993 through December 2005.
- All patients in whom breast MRI was performed were "assumed" to have been pre-operatively staged with breast MRI.
- In the case of multifocal lesions the largest diameter of the total area with tumor foci was recorded. If this information was not available, the size of the largest focus was recorded.
- There was a statistically significant difference in age between the groups. The MR- group's age ranged from 48 to 74 and the MR+ group's age ranged from 46 to 66. There may have been other imbalances in the groups that could contribute to operative decisions.
- Authors state that, "We did not observe any significant difference in hormone receptor expression. Although the Her2/Neu receptor was more often over-expressed in the MR- group, the expression was only assessed in 155 patients and the difference did not reach statistical significance." However that represents missing data on 42% of patients.
- Authors acknowledge that, "Because studies have shown that the rate of local recurrences is higher in patients who undergo re-excisions than in patients who are initially successfully treated, our study suggests that preoperative MRI in patients with ILC has the potential to improve local control and therefore survival. However, this negative effect from reexcisions was not evident from other studies, and is therefore uncertain."
- Authors state that, "We agree that the most valid proof of improved outcome is a clear reduction in breast cancer mortality, following a reduction of local recurrence. Such evidence in patients with ILC is still lacking, we neither

assessed local recurrence nor survival in this study. However, due to improving overall diagnosis and treatment current recurrence rates have dropped to approximately 0.6–1% per year [43]. Furthermore, ILC is a relatively infrequent breast cancer, so large studies to evaluate the impact of preoperative MRI on recurrence and survival will be acquired over a very long time span. Consequently, surgical approaches and adjuvant therapies will have continued to develop and an effect on outcome using these terms may be difficult to interpret as they are prone to bias."

- Authors hypothesize that patients who were unlikely to undergo BCS based on psychological factors, might be also less likely to undergo preoperative MRI.
- MRI protocols were not uniform in the study period and other changes have occurred in spatial resolution and the addition of other sequences. This study evaluated only use of contrast enhanced breast MRI.
- Not extrapolatable to other forms of cancer.

O'Neill 09
Psychological Impacts Surrounding Use of MRI for Women with Breast Cancer or at High-risk of Breast Cancer
O'Neill 09
Citation: O'Neill SM, Rubinstein WS, Sener SF, Weissman SM, Newlin AC, West DK, Ecanow DB, Rademaker AW, Edelman RR. Psychological impact of recall in high-risk breast MRI screening. Breast Cancer Res Treat. 2009 May;115(2):365-71. Epub 2008 Jul 26. PubMed PMID: 18661230.
Manufacture Involvement: No
Reviewer Grade
Delfini Grade: BU
AHRQ Grade: Medium risk of bias

Delfini Evidence Statement:
The evidence might be sufficient to use in making health care decisions; however, there remains sufficient uncertainty that the evidence cannot fully reach a Grade B and the uncertainty is not great enough to fully warrant a Grade U. Study quality is such that it appears likely that the evidence is sufficient to use in making health care decisions; however, there are some study issues that raise continued uncertainty. Health care decision-makers should be fully informed of the evidence quality.

PUBLISHED ABSTRACT SECTIONS WITH REVIEWER COMMENTS (RC)

PURPOSE: To address the widespread concern that false-positive results during breast MRI screening may have adverse psychological effects.

METHODS: Impact of Event Scale measurements in 103 high-risk women enrolled in a longitudinal MRI screening study and comparison of subjects with normal results vs. those with prior recall events.

RC: **Population notes**: All came from single site. Population was all Caucasian, with the exception of one Asian woman; 46% had Ashkenazi Jewish ancestry. Age range 27 to 76, average 50.8 years. History of breast cancer = 60%, known BRCA 1 or 2 mutation 16%, and BRCA carriers with a history of breast cancer 2%. Family history of breast cancer = 95%. High risk solely through Gail or BRCAPRO models = 25%. Authors point out that, "…the women who self-selected for this study would have monitoring styles and be highly conscientious," and thus, may explain why mutation carriers experienced an increase in cognitive avoidance symptoms, yet still complied with getting their next scan.

High risk was defined as a known BRCA1 or BRCA2 mutation, a >= 3.5% 5-year risk 5-year risk of breast cancer based on the Gail or BRCAPRO model, and/ or a personal history of invasive or non-invasive breast cancer.

Measurement notes: Subjects completed an Impact of Event Scale (IES) questionnaire immediately before the baseline MRI and each subsequent scan. The IES is a 15 item instrument used to measure stress in response to a specific event, in this case how they felt about breast cancer. The Intrusion subscale contains seven items and the Avoidance subscale contains eight items scored with point values of 0 = not at all, 1 = rarely, 3 = sometimes, 5 = often. The total IES score ranges from 0 to 75, with a higher score indicating more breast cancer specific distress. The authors provide support that this may be appropriate instrument for this kind of assessment.

Participants with BIRADS 1 or 2 results were scheduled for MRI 12 months later. Those with BIRADS 3 results were scheduled for a 6 month interval MRI or further evaluation at the discretion of the radiologist. Those with BIRADS 4 and 5 results underwent diagnostic evaluation including biopsy. If a malignancy was detected the subject was withdrawn from the study; data up to withdrawal are included in the analysis. Follow-up extended 1 year beyond the last MRI scan.

Loss: Roughly 10% did not comply with 6 month MRI; none developed breast cancer within a year of follow-up.

RESULTS: Of 189 MRI scans performed, 64 (34%) prompted further evaluation. Subjects with previously abnormal results had significantly higher Avoidance scores at the time of their second MRI. Mean baseline Avoidance score was 7.5 (N=103). A score of 7.5 would be rated as "subclinical" in severity. Mean score increased to 9.9 at MRI 2 (N=66) and) 10.4 at MRI 3 (N=17). Mean changes were statistically significant and indicate some increase in psychological stress. Multivariate analysis showed this was driven by the greater number of BRCA1/2 carriers in that group but was not related to screening recall.

RC: Limitations: In addition to external validity issues, authors cite the following key issues—

- Small sample size
- Highly motivated women
- Willingness to try new screening modality
- Did not evaluate the psychological effect of breast biopsies
- 4 women did not comply with their recall recommendation (although had "extremely low distress at baseline").

CONCLUSIONS: Practitioners' concerns about the high false positive rate of breast MRI may not be matched by actual psychological effects in most high-risk women.

RC: Authors state that, "…we found little increase in psychological disturbance in a group of high-risk women whose MRI results prompted recall."

Based on this study the **evidence is insufficient for concluding meaningful psychological harm**. However, uncertainty about the changes in Avoidance scores reported in this study and external validity issues render findings applicable to a limited population.

Pengel 09
MRI and Changes in Operative Management
Citation: Pengel KE, Loo CE, Teertstra HJ, Muller SH, Wesseling J, Peterse JL, Bartelink H, Rutgers EJ, Gilhuijs KG. The impact of preoperative MRI on breast-conserving surgery of invasive cancer: a comparative cohort study. Breast Cancer Res Treat. 2009 Jul;116(1):161-9. Epub 2008 Sep 21. PubMed PMID: 18807269.
Manufacture Involvement: No
Reviewer Grade
Delfini Grade: BU
AHRQ Grade: Medium risk of bias

Delfini Evidence Statement:
The evidence might be sufficient to use in making health care decisions; however, there remains sufficient uncertainty that the evidence cannot fully reach a Grade B and the uncertainty is not great enough to fully warrant a Grade U. Study quality is such that it appears likely that the evidence is sufficient to use in making health care decisions; however, there are some study issues that raise continued uncertainty. Health care decision-makers should be fully informed of the evidence quality.

PUBLISHED ABSTRACT SECTIONS (WHITE) WITH REVIEWER COMMENTS & KEY POINTS OF STUDY (RC IN GREY)

AIM: To assess whether preoperative contrast-enhanced magnetic resonance imaging (MRI) of the breast influences the rate of incomplete tumor excision.

METHODS: In a cohort of 349 women with invasive breast cancer, patients eligible for breast-conserving therapy (BCT) on the basis of conventional imaging and palpation only (N = 176) were compared to those who had an additional preoperative MRI (N = 173). Multivariate analysis was applied to explore associations with incomplete tumor excision.

RC:

- Observational study
- Dates: March 2002 through July 2004
- Population Information:
    - All eligible women included. Only primary of ductal carcinoma in site (DCIS) among those excluded.
    - At baseline the MRI group consisted of 173 women with 175 tumors (2 contra-lateral tumors prior to MRI). The non-MRI group consisted of 176 women with 180 breast tumors (4 contra-lateral tumors).
    - There was a statistically significant difference between the groups in age(P = 0.02) and there may have been other differences in unreported prognostic variables.
        - MRI Group: The mean age was 56.1 years, standard deviation (SD) 9.9 years (range: 28– 82)
        - Non-MRI Group: 59.6 years, SD 11.1 years (range: 31–89)
        - Authors analyzed the allocation procedure but could not find an explanation for this finding. They performed multivariate analysis, taking the differences in age into account. They state that, "Premenopausal women are at increased risk of local recurrence because of dense breast tissue (resulting in difficulty to visualize tumor extent) and increased tumor aggressiveness. Nonetheless, despite the younger age of the women in the MRI group, this group still showed more complete excisions of infiltrating ductal carcinoma IDC than the non- MRI group. This effect was not caused by larger excision volumes in the MRI group compared to the non-MRI group."
    - No significant differences were found between the tumor characteristics in the two groups.
        - Invasive ductal carcinoma (IDC) in 274 (77.2%) of the cases
        - Invasive lobular carcinoma (ILC) was found in 53 (14.9%) of the cases
- Detection and staging of breast cancer was performed by mammography, ultrasonography, and physical examination. Ultrasonography was also used to detect pathological loco-regional lymph nodes. Proof of breast cancer was obtained using fine-needle aspiration (FNA) or core biopsy. Treatment plans were established in consensus by a multi-disciplinary team of breast cancer specialists (radiologists, surgeons, medical oncologists, radiation oncologists, pathologists, and nurse practitioners).
- All eligible patients were included in the MRI group unless they refused to participate, could not be imaged by MRI prior to the scheduled surgery date or had contraindications for MRI such as claustrophobia.
- Quality control procedures included the establishing of study guidelines, multi-disciplinary teams and use of radiologists, surgeons and pathologists experienced in breast cancer.

RESULTS: MRI detected larger extent of breast cancer in 19 women (11.0%), leading to treatment change: mastectomy (8.7%) or wider excision (2.3%). Tumor excision was incomplete in 22/159 (13.8%) wide local excisions in the MRI group and in 35/180 (19.4%) in the non-MRI group (P = 0.17). Stratified to tumor type, incompletely excised infiltrating ductal carcinoma (IDC) was significantly associated with absence of MRI: 11/136 (8.1%) versus 2/126 (1.6%) (MRI present) (P = 0.02). No significant factors explained incomplete excision of other tumor types.

RC:

- In four cases (2.3%) a wider excision was performed than initially planned. Three women (1.7%) were found to have additional contra-lateral breast cancer, (not visible at conventional imaging). These MRI-detected contra-lateral tumors were not included in the current study. In one woman with a bilateral tumor the treatment was changed to bilateral mastectomy, according to the wish of the patient. The other two women underwent bilateral BCT. A total of 157 women with 159 tumors continued with wide-local excision.
- In the entire cohort no significant difference in incomplete excision between the MRI and the non-MRI group was found (P = 0.17). Further stratification by subset analysis showed significant association between preoperative MRI and reduced rates of incompletely excised infiltrating ductal carcinoma (IDC) (P = 0.02). Authors state that, "These findings may provide input to future studies investigating the potential benefit of preoperative MRI in subgroups of patients." Subset analysis prone to chance findings.

CONCLUSION: Preoperative MRI did not significantly affect the overall rate of incomplete tumor excision, but it yielded significantly lower rate of incompletely excised IDC. The reduction of incomplete excisions after MRI was smaller than the rate of a prior treatment change incurred by MRI.

RC:

- Study is not a randomized controlled trial which authors acknowledge is the standard study design for medical intervention studies.
- A second impact of MRI appears to be the high accuracy at which the extent and location of IDC is visualized. This provided the surgeons with a better preoperative assessment resulting in reduced rates of incompletely excised IDC. Despite observations from other studies demonstrating superior sensitivity of MRI for ILC compared to that of conventional breast imaging we were unable to translate these findings to reduced rates of incompletely excised ILC. Several explanations may exist. First, the number of patients with ILC was relatively small in our cohort. Secondly, all patients in our study were eligible for BCT on the basis of conventional imaging thus excluding tumors larger than 3 cm that were also included in other studies. Thirdly, evidence of multi-focal disease elsewhere in the breast may be difficult to extract from the cut margins of the WLE specimens at histopathology due to the finite tissue sampling and the typically diffuse multi-nodular pattern of growth of ILC Some of these considerations also hold for DCIS. Moreover, variable sensitivity of MRI for the detection of pure DCIS has been observed in other studies
- Single site Dutch study. Surgical choices may have cultural context which may not reflect that of the US.
- The authors state [citations excluded] that, "The impact of preoperative MRI appeared twofold. **Firstly women with more extensive pathology-proven disease were filtered away from the standard BCT eligibility and thus received a more extensive surgical treatment (mastectomy or a wider excision).** The increased mastectomy rate in the MRI group raises the concern that MRI leads to over-treatment. Indeed, increased mastectomy rates were also reported in other studies. It is likely that additional malignant disease also occurred in the non-MRI group. This assumption is supported by studies that reported more extensive disease in diverse groups of breast tumors. Consequently, a considerable part of undetected multi-focal tumor may be controlled by adjuvant treatment such as radiotherapy. Nonetheless, it is also known that radiotherapy is ineffective to eradicate large residual tumor burden. It remains to be proven whether conversion of therapy to mastectomy on the basis of additional MRI-detected disease has impact on the 15–20-year local recurrence rates after BCT. This may be of particular concern in younger patients where the local recurrence rate is approximately twice as large as in older patients. In a retrospective analysis, Fischer and colleagues reported that preoperative MRI reduced the incidence of local recurrence. Impact of preoperative MRI on surgical precision was not addressed. Solin and colleagues reported that the use of MRI in the staging of the patients was not associated with an improvement in local control after BCT. One of the study limitations, indicated by the authors, was a significantly lower age of women in the MRI group, which makes differences in local recurrence difficult to interpret. In contrast to Fischer et al., Solin and colleagues took differences in age and adjuvant treatment into account in their analysis. Local recurrence was not an end-point of our current study.

  "A second impact of MRI appears to be the high accuracy at which the extent and location of IDC is

visualized. This provided the surgeons with a better preoperative assessment resulting in reduced rates of incompletely excised IDC. Despite observations from other studies demonstrating superior sensitivity of MRI for ILC compared to that of conventional breast imaging, we were unable to translate these findings to reduced rates of incompletely excised ILC. Several explanations may exist. First, the number of patients with ILC was relatively small in our cohort. Secondly, all patients in our study were eligible for BCT on the basis of conventional imaging thus excluding tumors larger than 3 cm that were also included in other studies. Thirdly, evidence of multi-focal disease elsewhere in the breast may be difficult to extract from the cut margins of the WLE specimens at histopathology due to the finite tissue sampling and the typically diffuse multi-nodular pattern of growth of ILC. Some of these considerations also hold for DCIS. Moreover, variable sensitivity of MRI for the detection of pure DCIS has been observed in other studies."

- Authors acknowledge that "…potential differences in how MRI findings are incorporated into clinical decision-making may lead to differences in outcome and cost-benefit between hospitals.

Perazella 07
MRI Breast Project
Safety Gadolinium
Citation: Perazella MA, Rodby RA. Gadolinium use in patients with kidney disease: a cause for concern. Semin Dial. 2007 May-Jun;20(3):179-85. Review. PubMed PMID: 17555477.

Manufacture Involvement:
Reviewer Grade
Delfini Grade: **U**
AHRQ Risk of Bias Rating: High
Evidence Statement: There is sufficient uncertainty that caution is urged regarding its use in making health care decisions.

PUBLISHED ABSTRACT SECTIONS WITH REVIEWER COMMENTS (RC)
Gadolinium is widely used as a magnetic resonance imaging contrast agent and is considered to have a good overall safety profile. Recently, both renal and extra-renal toxicities have been reported following exposure to gadolinium in patients with underlying kidney disease. Gadolinium- related contrast-induced nephropathy appears to be a risk in patients with advanced kidney disease and especially those with diabetic nephropathy. Even more concerning is the strong association of gadolinium with nephrogenic systemic fibrosis (NSF), a devastating fibrosing disorder of the skin and other systemic organs. Although cause and effect have not been proven for the NSF-gadolinium link, the impaired renal elimination of gadolinium in patients with kidney disease and the instability of gadoliniumchelate binding may expose tissues to toxic free Gd3+ and promote this fibrosing disorder. Caution should be exercised when utilizing gadolinium as a contrast agent in patients with advanced CKD or ESRD.
RC: Methodological Issues: • "Critical review" without search or inclusion criteria. • Expert opinion regarding safety in CKD patients.

Plevritis 06
Economic Analysis
Citation: Plevritis SK, Kurian AW, Sigal BM, Daniel BL, Ikeda DM, Stockdale FE, Garber AM. Cost-effectiveness of screening BRCA1/2 mutation carriers with breast magnetic resonance imaging. JAMA. 2006 May 24;295(20):2374-84. PubMed PMID: 16720823.
Manufacture Involvement: No
Reviewer Grade
Delfini Grade: Grade BU for cost; Grade U for cost effectiveness
AHRQ Grade: Medium risk of bias for cost; High risk of bias for cost effectiveness

Delfini Evidence Grades:

Grade BU: The evidence might be sufficient to use in making health care decisions; however, there remains sufficient uncertainty that the evidence cannot fully reach a Grade B and the uncertainty is not great enough to fully warrant a Grade U.

Grade U: There is sufficient uncertainty that caution is urged regarding its use in making health care decisions.

PUBLISHED ABSTRACT SECTIONS (WHITE) WITH REVIEWER COMMENTS & KEY POINTS OF STUDY (RC IN GREY) [References removed]

CONTEXT: Women with inherited BRCA1/2 mutations are at high risk for breast cancer, which mammography often misses. Screening with contrast-enhanced breast magnetic resonance imaging (MRI) detects cancer earlier but increases costs and results in more false-positive scans.

RC:
- US-based analysis
- Modeled analysis
- Comparison of MRI to mammography (it appears that digital mammography was not modeled) under protocols of no screening, annual mammography from ages 25 to 69 years, and annual mammography from ages 25 to 69 years plus annual MRI for specific age groups
- Perspective = societal
- All costs were updated to US 2005 figures with a discount rate of an annual 3%.

OBJECTIVE: To evaluate the cost-effectiveness of screening BRCA1/2 mutation carriers with mammography plus breast MRI compared with mammography alone.

DESIGN, SETTING, AND PATIENTS: A computer model that simulates the life histories of individual BRCA1/2 mutation carriers, incorporating the effects of mammographic and MRI screening was used. The accuracy of mammography and breast MRI was estimated from published data in high-risk women. Breast cancer survival in the absence of screening was based on the Surveillance, Epidemiology and End Results database of breast cancer patients diagnosed in the prescreening period (1975-1981), adjusted for the current use of adjuvant therapy. Utilization rates and costs of diagnostic and treatment interventions were based on a combination of published literature and Medicare payments for 2005.

RC:
- A simulated cohort of female 25-year old BRCA 1/2 mutation carriers, born in 1980, was followed over their lifetimes starting in 2005. These women had no prior breast cancer history and had not undergone prophylactic mastectomy or chemoprevention. Other assumptions used were reported.
- Authors made heavy reliance on published data.
- Screening-related outcomes were modeled using natural history of the disease using a mathematical model of the natural history of invasive breast cancer developed previously by the authors derived from SEER data including distributions for detected tumor size and stage in BRCA 1/2 mutation carriers not undergoing screening stratified by age and tumor grade.
- Tumor size-dependent threshold was used, assuming that all tumors larger than 5 mm are detectable by MRI and 1 CM for tumors that are mammographically visible. However, Taneja 09 states that, "…data from the trials of dual screening indicate that tumors > 5 mm are missed by MRI and that the median size of invasive tumors detected by screening XM is somewhat greater than 10 mm."
- Digital mammography appears not to have been used in the model.
- The model was designed to produce estimates of sensitivity, specificity, (Leach 05) lead time and overdiagnosis rates.

- In the case of diagnosis of unilateral cancer, bilateral mastectomy was assumed for 50% of women over 50 and 40% for younger women, with the remainder treated by unilateral mastectomy; breast reconstruction surgery was assumed for all.
- Chemoprevention with prophylactic tamoxifen or other agents was not included in this analysis.
- Ductal carcinoma in situ (DCIS) was not included as a separate disease state in the model due to lack of evidence in this population
- Costs of screening and treatment included costs of time lost from work.
- Authors cite lack of quality of life data.

MAIN OUTCOME MEASURES: The survival benefit, incremental costs, and cost-effectiveness of MRI screening strategies, which varied by ages of starting and stopping MRI screening, were computed separately for BRCA1 and BRCA2 mutation carriers.

RC:

- Sensitivity analyses were performed.
- Because the cost-effectiveness of MRI was evaluated relative to mammography, cost-effectiveness of MRI in this analysis is dependent upon effectiveness of mammography.
- In this analysis, MRI was reported as being—
    - Most sensitive to breast cancer risk
    - Sensitive to potential for overdiagnosis bias
    - Sensitive to both cost of MRI and discount rate
    - Potentially affected by changes in treatment — breast conserving therapy was not included in this analysis, for example
    - More cost-effective under the following conditions—
        - Breast cancer risk increases
        - Detection of cancers so early that chemotherapy can be reduced (however, no evidence is cited to support if this is possible or true)
        - If reassurance of a negative MRI produces greater gains in quality of life over that produced by a negative mammogram, especially for BRCA 2 carriers
    - Less cost-effective under the following conditions—
        - Breast cancer risk decreases
    - Little affected by plausible variations in mean tumor volume doubling time, ovarian cancer survival, and the detection threshold of MRI

RESULTS: Screening strategies that incorporate annual MRI as well as annual mammography have a cost per quality-adjusted life-year (QALY) gained ranging from less than 45,000 dollars to more than 700,000 dollars, depending on the ages selected for MRI screening and the specific BRCA mutation. Relative to screening with mammography alone, the cost per QALY gained by adding MRI from ages 35 to 54 years is 55,420 dollars for BRCA1 mutation carriers, 130,695 dollars for BRCA2 mutation carriers, and 98,454 dollars for BRCA2 mutation carriers who have mammographically dense breasts.

RC:

- May be inaccurate because RCTs for effectiveness are lacking

CONCLUSIONS: Breast MRI screening is more cost-effective for BRCA1 than BRCA2 mutation carriers. The cost-effectiveness of adding MRI to mammography varies greatly by age.

RC:

- Threshold used was $100,000 per QALY gained.

Sardanelli 04
Accuracy Dense Breasts
(INCLUDED IN LORD 07 META-ANALYSIS)
Citation: Sardanelli F, Giuseppetti GM, Panizza P, Bazzocchi M, Fausto A, Simonetti G, Lattanzio V, Del Maschio A; Italian Trial for Breast MR in Multifocal/Multicentric Cancer. Sensitivity of MRI versus mammography for detecting foci of multifocal, multicentric breast cancer in Fatty and dense breasts using the whole-breast pathologic examination as a gold standard. AJR Am J Roentgenol. 2004 Oct;183(4):1149-57. PubMed PMID: 15385322.

Manufacture Involvement:
Reviewer Grade
Delfini Grade: **BU**
AHRQ Risk of Bias Rating: Medium

PUBLISHED ABSTRACT SECTIONS WITH REVIEWER COMMENTS (RC)

OBJECTIVE. Our aim was to compare the effectiveness of mammography and MRI in the detection of multifocal, multicentric breast cancer.
SUBJECTS AND METHODS. Ninety patients with planned mastectomies (nine bilateral) underwent mammography and dynamic gadolinium-enhanced MRI. Off-site reviewers aware of the entry criterion (planned mastectomy) evaluated both examinations for the presence of malignant foci, recording the density pattern on mammography. The gold standard was pathologic examination of the whole excised breast (slice thickness, 5 mm).
RESULTS. Of 99 breasts, pathologic findings revealed 52 unifocal, 29 multifocal, and 18 multicentric cancers for a total of 188 malignant foci (158 invasive and 30 in situ). Overall sensitivity was 66% (124/188) for mammography and 81% (152/188) for MRI ($p < 0.001$); 72% (113/ 158) and 89% (140/158) for invasive foci ($p < 0.001$); and 37% (11/30) and 40% (12/30) for in situ foci ($p > 0.05$, not significant), respectively. Mammography and MRI missed 64 and 36 malignant foci, respectively, with median diameters of 8 and 5 mm ($p = 0.033$) and an invasive–noninvasive ratio of 2.4:1 (45:19) and 1.0:1 (18:18) ($p = 0.043$), respectively. The overall positive predictive value (PPV) was 76% (124/164) for mammography and 68% (152/222) for MRI (not significant). In breasts with an almost entirely fatty pattern, sensitivity was 75% for mammography and 80% for MRI (not significant), and the PPV was 73% and 65% (not significant), respectively. In breasts with fibroglandular or dense pattern, the sensitivity was 60% and 81% ($p < 0.001$), and the PPV was 78% and 71% (not significant), respectively.
CONCLUSION. MRI was more sensitive than mammography for the detection of multiple malignant foci in fibroglandular or dense breasts. Mammography missed larger and more invasive cancer foci than MRI. A relatively low PPV was a problem for both techniques.

RC:
Diagnostic Issues:

- Multicenter observational study
- 18 European Centers
- Patients: 18 years old or older of any race, with proven breast cancer and a planned mastectomy (proposed by the surgeon or oncologist or both or based on the patient's preference)
- The reviewers were aware of the entry criterion (planned mastectomy) but were blinded to all patient data and to the results of the pathologic examination.
- The density pattern on mammography was recorded as almost entirely fatty, scattered fibroglandular or heterogeneously dense, or extremely dense.
- A number of patients among the 153 enrolled patients were not eligible for evaluation. A total of 42 patients were excluded because mastectomy was ultimately not performed (some patients opted for presurgical adjuvant chemotherapy), resulting in the absence of a pathologic gold standard for the entire breast or because the mammography, MRI, or pathologic examinations were either incomplete or subject to imaging artifacts (e.g., patient movement between the pre- and postcontrast MRI). An additional 21 patients were excluded from analysis at the central off-site unit because of protocol violations during MR image acquisition (e.g., a slice thickness of 4 mm rather than 3 mm in patients with large breasts). No exclusion from data analysis was due to the results of mammography or MRI.

Schwartz 00
Psychological Impacts Surrounding Use of MRI for Women with Breast Cancer or at High-risk of Breast Cancer
Citation: Schwartz LM , Woloshin S , Sox HC , Fischhoff B , Welch HG . US women's attitudes to false positive mammography results and detection of ductal carcinoma in situ: cross sectional survey . BMJ 2000 ; 320 : 1635 – 1640 .

Manufacture Involvement: No information
Reviewer Grade
Delfini Grade: U
AHRQ Grade: High risk of bias

Delfini Evidence Statement:
There is sufficient uncertainty that caution is urged regarding its use in making health care decisions.

PUBLISHED ABSTRACT (WHITE) WITH REVIEWER COMMENTS & KEY POINTS OF STUDY (RC IN GREY)

Objective To determine women's attitudes to and knowledge of both false positive mammography results and the detection of ductal carcinoma in situ after screening mammography.
Design Cross sectional survey.
Setting United States.
Participants 479 women aged 18-97 years who did not report a history of breast cancer.
Main outcome measures Attitudes to and knowledge of false positive results and the detection of ductal carcinoma in situ after screening mammography.
Results Women were aware that false positive results do occur. Their median estimate of the false positive rate for 10 years of annual screening was 20% (25th percentile estimate, 10%; 75th percentile estimate, 45%). The women were highly tolerant of false positives: 63% thought that 500 or more false positives per life saved was reasonable and 37% would tolerate 10 000 or more. Women who had had a false positive result (n = 76) expressed the same high tolerance: 39% would tolerate 10 000 or more false positives. 62% of women did not want to take false positive results into account when deciding about screening. Only 8% of women thought that mammography could harm a woman without breast cancer, and 94% doubted the possibility of non-progressive breast cancers. Few had heard about ductal carcinoma in situ, a cancer that may not progress, but when informed, 60% of women wanted to take into account the possibility of it being detected when deciding about screening.
Conclusions Women are aware of false positives and seem to view them as an acceptable consequence of screening mammography. In contrast, most women are unaware that screening can detect cancers that may never progress but feel that such information would be relevant. Education should perhaps focus less on false positives and more on the less familiar outcome of detection of ductal carcinoma in situ.

RC:
- Observational study of attitudes regarding mammography (not MRI) in women without history of breast cancer.
- Useful information.

Scomersi 10
Change in Treatment Plans
Reference: Scomersi S, Urbani M, Tonutti M, Zanconati F, Bortul M. Role of magnetic resonance imaging in managing selected women with newly diagnosed breast cancer. Breast. 2010 Apr;19(2):115-9. Epub 2010 Jan 27. PubMed PMID: 20106663.

Abstract
The purpose of this study is evaluation of therapeutic impact of magnetic resonance imaging (MRI) in breast cancer patients that cannot be imaged adequately with traditional radiology: dense breasts, microcalcifications suspicious for carcinoma in situ or discordance between mammography and ultrasound. A review was performed of 493 patients' records: determination of breast MRI effect on clinical management was made for the selected 70 cases by analysing pre-MRI and post-MRI therapeutic plans. Analysis of final pathology was useful to determine if the change in surgical plan prompted by MRI was appropriate. Breast MRI added clinical information in 52.9% of patients that resulted in 44.3% of management changes that were judged as appropriate in 83.9% of cases. Breast MRI provides additional useful information, but causes more extensive surgery (40%) with no proven prognostic benefit. MRI should be considered optional in the clinical staging of breast cancer and performed in selected cases. PMID: 20106663 [PubMed - in process]

Appraisal from abstract because design (chart review) indicates grade U

Evidence Grade:
Delfini Grade: U
AHRQ Risk of Bias: High
Delfini Evidence Statement:
There is sufficient uncertainty that caution is urged regarding its use in making health care decisions.

Shellock 06

Reference	Abstract	Comments
Shellock FG, Parker JR, Pirovano G, Shen N, Venetianer C, Kirchin MA, Spinazzi A. Safety characteristics of gadobenate dimeglumine: clinical experience from intra- and interindividual comparison studies with gadopentetate dimeglumine. J Magn Reson Imaging. 2006 Dec;24(6):1378-85. Erratum in: J Magn Reson Imaging. 2007 Jul;26(1):217. PubMed PMID: 17078095.	Numerous gadolinium-based MRI contrast agents have been approved for clinical use in the United States. The most recent review of gadolinium-based agents included 79 observational studies (some patient with hepatic or renal impairment or coronary artery disease) who received various preparations of gadolinium chelates in conjunction with MRI imaging. Most gadolinium-based agents are similar with regard to their physical properties, mode of action, and general safety profiles. The review compared adverse events reported in patients receiving contrast agents to placebo and included postmarketing safety surveillance data and totaled more than 1.5 million applications of gadolinium agents. The reported adverse event rates were similar in the contrast agent group (13%) and placebo group (17%). Serious adverse events were rarely reported and included dyspnea, nausea, urticaria, hypotension, and anaphylactoid reactions. The authors reviewed previous studies and reported that none showed a discernible difference between the various gadolinium-based MRI contrast agents in terms of the incidence or type of adverse event reported. The authors found one report of "spurious hypocalcemia" with an observed decrease from normal serum calcium levels in as many as 16% of patients given preparations of the agent gadodiamide.	Narrative Review Delfini evidence grade: Grade U AHRQ Rating of Bias: High

Solin 08

MRI High Risk Women

Solin LJ, Orel SG, Hwang WT, Harris EE, Schnall MD. Relationship of breast magnetic resonance imaging to outcome after breast-conservation treatment with radiation for women with early-stage invasive breast carcinoma or ductal carcinoma in situ. J Clin Oncol. 2008 Jan 20;26(3):386-91. PubMed PMID: 18202414

Abstract

Purpose To determine the relationship of breast magnetic resonance imaging (MRI) to outcome after breast-conservation treatment (BCT) with radiation for women with early-stage invasive breast carcinoma or ductal carcinoma in situ.

Patients and Methods A total of 756 women with early stage invasive breast carcinoma or ductal carcinoma in situ underwent BCT including definitive breast irradiation during 1992 to 2001. At the time of initial diagnosis and evaluation, routine breast imaging included conventional mammography. Of the 756 women, 215 women (28%) had also undergone a breast MRI study, and 541 women (72%) had not undergone a breast MRI study. The median follow-up after treatment was 4.6 years (range, 0.1 to 13.5 years).

Results For the women with a breast MRI study compared with the women without a breast MRI study, there were no differences in the 8-year rates of any local failure (3% *v* 4%, respectively; *P* =.51) or local-only first failure (3% *v* 4%, respectively; *P* =.32). There were also no differences between the two groups for the 8-year rates of overall survival (86% *v* 87%, respectively; *P* =51), cause-specific survival (94% *v* 95%, respectively; *P* =.63), freedom from distant metastases (89% *v* 92%, respectively; *P* =.16), or contralateral breast cancer (6% *v* 6%, respectively; *P* =.39).

Conclusion The use of a breast MRI study at the time of initial diagnosis and evaluation was not associated with an improvement in outcome after BCT with radiation.

Delfini Grade U

AHRQ Risk of Bias Grade: High

The evidence is not sufficient making health care decisions; the uncertainty about estimate of effect is high and the evidence is insufficient to use in making health care decisions.

Reviewer Comment:

- This study reports that the use of breast MRI was not associated with an improvement in outcomes after BCT with radiation: overall survival, cause-specific survival, freedom from distant metastases, local control, or contralateral breast cancer. The authors conclude that MRI is not globally indicated for all patients with early-stage breast cancer at the time of initial diagnosis and evaluation.

Study Type

- Retrospective, single-center, cohort study, U Penn.

Funding Source

Details:

- Supported in part by a grant from the Cancer Research Foundation.

Aim

Details	To determine the relationship of breast magnetic resonance imaging (MRI) to outcome after breast-conservation treatment (BCT) with radiation for women with early-stage invasive breast carcinoma or ductal carcinoma in situ.

Outcome Measures

Details	Primary Outcome(s) ▪ Outcomes for overall survival, cause-specific survival, freedom from distant metastases, local control, and contralateral breast cancer.

Population Inclusions Exclusions and Interventions

Details	• American Joint Commission on Cancer (AJCC) clinical and pathologic stage 0, I, or II disease

	(TisN0M0, T1N0M0, T2N0M0, T1N1M0, or T2N1M0) • Unilateral disease at presentation; invasive breast carcinoma or DCIS of the breast; definitive locoregional management using BCT consisting of breast conserving surgery followed by definitive breast irradiation; definitive breast irradiation at the Hospital of the University of Pennsylvania; definitive breast irradiation to a total dose of 60 Gy or more; if performed, breast MRI study performed before definitive breast irradiation; treatment dates of 1992 to 2001; no prior or concurrent malignancy (breast or other site), except for nonmelanoma skin cancer; and for the patients with invasive breast carcinoma, pathologic axillary lymph node staging performed. • The median age for the patients with a breast MRI study was 53 years (mean, 53 years; range, 25 to 85 years), and the median age for the patients without a breast MRI study was 56 years (mean, 57 years; range, 27 to 89 years). The patients with a breast MRI study also had slightly more favorable tumor characteristics in terms of clinical tumor size, when known, and pathologic axillary lymph node staging. Routine breast imaging included conventional mammography, with correlation ultrasound as indicated. • Of the study population of 756 patients, 215 patients (28%) had also undergone a breast MRI study at the time of initial diagnosis and evaluation of breast cancer, and 541 patients (72%) had not undergone a breast MRI study. • The surgical treatment included complete gross excision of the primary tumor. Re-excision of the primary tumor site was performed for 437 patients (58%). Pathologic axillary lymph node staging was performed for all patients with invasive carcinoma. Early in the study period, pathologic axillary staging was generally performed using a lower axillary lymph node dissection, and later in the study period, sentinel lymph node biopsy became more commonly used. Radiation treatment was delivered to all patients with definitive intent. The median dose was 46 Gy for the radiation treatment to the whole breast (mean_46.54 Gy; range, 44.75 to 50.4 Gy).A boost to the primary tumor site was delivered after radiation treatment to the whole breast for all patients, and the large majority of the boosts were delivered using electrons. Regional radiation was individualized as was chemotherapy.
N	756 women who underwent BCT

Diagnostic Issues

Threats	• Retrospective design: selection bias possible • No blinding • Not consecutive patients • Adjusted for differences in age, margin status, date of treatment and the use of systemic therapy. • Patients with unfavorable findings on MRI were excluded from the BCT group, rather than simply observed to determine the significance of the mammographically occult cancer.

Selected Authors' Conclusions:

- The major finding from the present study is that the use of breast MRI was not associated with an improvement in outcomes after BCT with radiation. These findings suggest that MRI is not globally indicated for all patients with early-stage breast cancer at the time of initial diagnosis and evaluation.
- Given the low baseline rate of local recurrence in those patients without a breast MRI study, a randomized study would require a substantially larger sample size than the 756 patients evaluated in the present study.
- Fischer 04 reported the outcome for 346 patients, of which only a subset (n=224;65%) had undergone BCT. The rate of local recurrence after BCT was lower for patients with a breast MRI compared with patients without a breast MRI (1.2% [one of 86] *v* 6.5% [nine of 138], respectively; *P*<001). However, this was a small study and only 65% underwent BCT. [REF: Fischer U, Zachariae O, Baum F, et al: The influence of preoperative MRI of the breasts on recurrence rate in patients with breast cancer. Eur Radiol 14:1725-1731, 2004]

RESULTS

- There were no differences between the two groups for overall survival, cause-specific survival, freedom from distant metastases, any local failure, local-only first failure, and contralateral breast cancer (all *P* >/=.16). The 8-year rate of any local failure was 3% for the patients with a breast MRI study and 4% for the patients without a breast MRI study (Fig 1). After adjusting for patient age and date of treatment, there continued to

be no difference between the two groups for overall survival, cause-specific survival, freedom from distant metastases, any local failure, local-only first failure, and contralateral breast cancer (all *P*>/=.19).

- For the subset of 136 patients with DCIS, the 8-year rate of any local failure was 6% versus 6%, respectively (P=.58). For the subset of 620 patients with invasive carcinoma, the 8-year rate of any local failure was 3% versus 3%, respectively, (P=.62).

Taneja 09
Economic Analysis

Citation: Taneja C, Edelsberg J, Weycker D, Guo A, Oster G, Weinreb J. Cost effectiveness of breast cancer screening with contrast-enhanced MRI in high-risk women. J Am Coll Radiol. 2009 Mar;6(3):171-9. PubMed PMID: 19248993.
Manufacture Involvement: One author is from Bayer HealthCare Pharmaceuticals. No further disclosures are provided.
Reviewer Grade
Delfini Grade: U
AHRQ Grade: High risk of bias

Delfini Evidence Statement:
There is sufficient uncertainty that caution is urged regarding its use in making health care decisions.

PUBLISHED ABSTRACT SECTIONS (WHITE) WITH REVIEWER COMMENTS & KEY POINTS OF STUDY (RC IN GREY) [References removed]

PURPOSE: The aim of this study was to estimate the cost effectiveness of breast cancer screening with contrast-enhanced magnetic resonance imaging (MRI), with and without adjunctive x-ray mammography (XM), compared with XM alone in high-risk women.

RC:
- US-based analysis
- Modeled analysis
- Perspective = healthcare system
- Costs were US 2005 price levels, discounted at an annual 3%.

MATERIALS AND METHODS: A model was developed to depict the consequences of screening with MRI and/or XM for cohorts of 10,000 women with BRCA1/2 mutations and women with other high-risk characteristics, respectively. The model predicted the number of women correctly and incorrectly diagnosed with each strategy and lifetime consequences in terms of additional care, patient utilities, life expectancy, and quality-adjusted life-years (QALYs). Cost effectiveness was calculated in terms of cost per QALY gained.

RC:
- At model entry, women were assumed to be a high risk for having previously undetected breast cancer, invasive or ductal carcinoma in situ (DCIS): BRCA 1/2 mutations or other high-risk characteristics (e.g., strong family history) associated with a lifetime risk for breast cancer of >= 20%.
- Age at model entry was 40 years.
- Women were assumed not to have previously undergone bilateral mastectomy.
- Screening histories were assumed similar to women enrolled in two clinical trials (Kriege 04 and Leach 05).
- All women were screened once at model entry with MRI, XM or both modalities.
- Women were classified into positive and negative groups (true and false) on the basis of whether they actually had breast cancer and the results of their screening. Prevalence of undiagnosed breast cancer, including DCIS, was based on pooled estimates of 4 clinical trials and NCI's Breast Cancer Risk Assessment Tool.
- Sensitivity and specificity were derived from Kriege 04 and Leach 05. They were assumed to be the same for a subgroup of women with BRCA 1/2 mutations and for the subgroup of other high risk women.
- Tumor size, characteristics and nodal status were derived from published studies and estimates in Plevritis 06. Authors note that there is a limited amount of published data on tumor sizes and the probability of nodal involvement for false-negative tumors, and further comment that this data is based on studies in which multiple annual screenings were performed.
- Authors cite other limitations due to assumption that no woman would be diagnosed with distant metastases and that all false-negative tumors would be diagnosed within one year.
- Risk of death from invasive breast cancer was estimated using a model by Michaelson 03. Risk of death for DCIS was derived from published data. Risk of death from all other causes was estimated from vital statistics reported by the National Center for Health Statistics, subtracting breast-cancer specific estimates.
- Costs included screening, follow-up diagnostic tests, treatment of local or regional disease and treatment of metastatic disease. No further details were reported, but authors cite published studies as references.

RESULTS: Among the 400 women (of 10,000) with BRCA 1/2 mutations and undiagnosed breast cancer, 361 cases would be detected with MRI and XM, 290 with MRI, and 160 with XM. False-positive results would total 1,526, 1,190,

and 528, respectively. Cost per QALY gained with MRI and XM compared with XM alone for women with BRCA1/2 mutations was $25,277. Among other high-risk women, cost per QALY gained with MRI and XM compared with XM alone varied depending on the prevalence of breast cancer, ranging from $45,566 (300 cases) to $310,616 (50 cases). The cost effectiveness of MRI alone compared with XM alone was similar.

RC:

- Model robustness is reported to have been tested by changing several key assumptions, however, further details were not provided.
- Cost-effectiveness of MRI screening was sensitive to—
    - assumed prevalence of undiagnosed breast cancer (strong)
    - Unit cost of MRI (strong)
    - Sensitivity of XM screening (moderate)
- Authors state that probably the greatest uncertainty in modeling involves the estimation of benefit of early detection in terms of prolonged survival as benefit has not been quantified in valid studies as of this writing.

CONCLUSION: Screening with MRI, alone or in combination with XM, in women with BRCA1/2 mutations is cost effective by current standards compared with XM alone. In women with other high-risk characteristics, MRI screening may also be cost effective, depending on the expected prevalence of undiagnosed breast cancer at the time of screening.

RC:

- We conclude that because of the absence of experimental evidence and the need for relying on models with unproven assumptions that cost effectiveness estimates are likely to be highly inaccurate. Cost to diagnose each additional case of breast cancer by adding MRI may be reliable.

Turnbull 10

MRI: Comparative Effectiveness of MRI Plus MRI and Changes in Operative Management

Citation: Turnbull L, Brown S, Harvey I, Olivier C, Drew P, Napp V, Hanby A, Brown J. Comparative effectiveness of MRI in breast cancer (COMICE) trial: a randomised controlled trial. Lancet. 2010 Feb 13;375(9714):563-71. PubMed PMID: 20159292.

Manufacture Involvement: No

Reviewer Grade: No single study grade assigned; see below.

IMPORTANT NOTE: This clinical trial includes information that is worth remarking on beyond the pre-specified endpoints of interest to the investigators. These potential conclusions are summarized here and tagged with a level of evidence statement that is irrespective of study grade which applies to the overall reliability of the study for the research question and authors' findings and conclusions. Pertinent background information to understanding these Reviewer Conclusions is provided below preceding the reviewer conclusions.

Background Overall

- Patients were randomized to Triple Assessment plus MRI versus Triple Assessment with no MRI. Triple assessment was defined as clinical, radiological (X-ray mammography and ultrasound) and pathological (fine-needle aspiration cytology or core biopsy) assessment.
- In the MRI group, out of the 58 patients who had a mastectomy, histology data appear to have been unavailable for 15 (26%) of patients and 11 (19%) did not have a biopsy.
- 93 percent of patients in the MRI group did not receive an MRI as compared to 99 percent of patients in the No MRI group being treated without receiving an MRI which is a differential migration of patients between groups.
- Study does not report mortality data.

Background to Review Conclusion 1

- Utilizing an Intention-to-Treat analysis conducted by the reviewers, there was a statistically significant difference in patients undergoing mastectomy in the MRI group versus the No MRI group even when excluding 3 patients in the MRI group who "chose to have a mastectomy," choice apparently meaning that mastectomy was not recommended for clinical management.
    - From Table 1, in the MRI group, 55 patients underwent a clinically recommended mastectomy out of 813 patients, 3 of whom chose a mastectomy for a total of 58 mastectomies (3 patients were lost to follow-up or had missing data out of a total 816 randomized).
    - In the No MRI group, 10 patients underwent a clinically recommended mastectomy out of 799 patients (8 patients were lost to follow-up or had missing data out of a total 807 randomized).
        - MRI 55/813 versus No MRI 10/799; P=0.0001, 95% CI (3.62 to 7.40 percent)
    - If true, the reviewers deem these results clinically significant as this may result in 4 to 8 more mastectomies, due to using MRI, than not using MRI when utilizing a triple assessment approach, outside a 5 percent play of chance. Some uncertainty is due to not knowing if there was an imbalance in lack or loss of histological data between the groups.

Reviewer Conclusion 1: Data are suggestive that Triple Assessment Plus MRI may increase the number of mastectomies performed as compared to assessment without MRI.
Delfini Grade for Level of Evidence for Conclusion: B to BU
AHRQ Grade for Bias: Medium risk of bias

Delfini Evidence Statement:
The evidence might be sufficient to use in making health care decisions; however, there remains sufficient uncertainty that the evidence cannot fully reach a Grade B and the uncertainty is not great enough to fully warrant a Grade U. Study quality is such that it appears likely that the evidence is sufficient to use in making health care decisions; however, there are some study issues that raise continued uncertainty. Health care decision-makers should be fully informed of the evidence quality.

Background to Reviewer Conclusion 2

- Utilizing an analysis method conducted by the reviewers which excluded patients who did not undergo further surgery or who were lost to follow-up (an appropriate safety population) and excluding the three patients in the MRI group who "chose" mastectomy, there was a statistically significant difference in patients who experienced

an avoidable initial mastectomy.

- From Table 3, in the MRI group, 16 patients were reported as having a pathologically avoidable initial mastectomy.
- In the No MRI group, 4 patients (less 0 who chose mastectomy) were reported as having a pathologically avoidable initial mastectomy.
  - MRI 16/813 versus No MRI 4/799 patients; P=0.01, 95% CI (0.39 to 2.54 percent)
- If true, the reviewers deem these results clinically significant as this may result in 1 to 3 more pathologically avoidable mastectomies per 100 screenings, due to using MRI, than not using MRI when utilizing a triple assessment approach, outside a 5 percent play of chance. Some uncertainty is due to not knowing if there was an imbalance in lack or loss of histological data between the groups.

Reviewer Conclusion 2: Data are suggestive that Triple Assessment Plus MRI may increase the number of pathologically avoidable mastectomies performed as compared to Triple Assessment No MRI.
Delfini Grade for Level of Evidence for Conclusion: B to BU
AHRQ Grade for Risk of Bias: Medium risk of bias

Delfini Evidence Statement:
The evidence might be sufficient to use in making health care decisions; however, there remains sufficient uncertainty that the evidence cannot fully reach a Grade B and the uncertainty is not great enough to fully warrant a Grade U. Study quality is such that it appears likely that the evidence is sufficient to use in making health care decisions; however, there are some study issues that raise continued uncertainty. Health care decision-makers should be fully informed of the evidence quality.

Background to Reviewer Conclusion 3

- Among their findings the authors report that, "309 patients (19%) underwent either a repeat operation or mastectomy at further operation within 6 months of randomisation, or a pathologically avoidable mastectomy at initial surgery, with a difference between the MRI and no MRI group of 0.58% (95% CI –3.24 to 4.40%)."
- However, a finding of non-significance raises the question whether there truly is no difference between groups or if there was an insufficient number of people to show a statistically significant difference if there was one. A review of the confidence intervals reveals that roughly 4 to 5 patients—a clinically significant number—within a 5 percent play of chance, could face a repeat operation or mastectomy at further operation within 6 months of randomisation or a pathologically avoidable mastectomy either way, thus these findings do not appear to be suggesting no difference between the groups, but rather are suggestive of inconclusive findings suggesting the study was insufficiently powered for this outcome.

Reviewer Conclusion 3: Authors' claims of no difference for repeat operation or mastectomy at further operation within 6 months of randomization, or a pathologically avoidable mastectomy at initial surgery appear to be unfounded. Results are inconclusive.
Delfini Grade for Level of Evidence for Conclusion: U
AHRQ Grade for Risk of Bias: High risk of bias

Delfini Evidence Statement:
There is sufficient uncertainty that caution is urged regarding its use in making health care decisions.

Background to Reviewer Conclusion 4

- Cost-effectiveness analysis first requires establishment of effectiveness. The basis for authors' findings has not been established through this study due to threats to validity and issues of clinical usefulness.

Reviewer Conclusion 4: Any authors' claims concerning cost-effectiveness are uncertain. Not able to draw conclusions on cost due to inconclusive findings.
Delfini Grade for Level of Evidence for Conclusion: U
AHRQ Grade for Risk of Bias: High risk of bias

Delfini Evidence Statement:

There is sufficient uncertainty that caution is urged regarding its use in making health care decisions.

PUBLISHED ABSTRACT SECTIONS (WHITE) WITH REVIEWER COMMENTS & KEY POINTS OF STUDY (RC IN GREY)

BACKGROUND: MRI might improve diagnosis of breast cancer, reducing rates of reoperation. We assessed the clinical efficacy of contrast-enhanced MRI in women with primary breast cancer.

METHODS: We undertook an open, parallel group trial in 45 UK centres, with 1623 women aged 18 years or older with biopsy-proven primary breast cancer who were scheduled for wide local excision after triple assessment. Patients were randomly assigned to receive either MRI (n=816) or no further imaging (807), with use of a minimisation algorithm incorporating a random element. The primary endpoint was the proportion of patients undergoing a repeat operation or further mastectomy within 6 months of random assignment, or a pathologically avoidable mastectomy at initial operation. Analysis was by intention to treat.

RC:

- Multicenter trial in 45 centers in the United Kingdom (UK).
- COMICE is reported through the Health Technology Assessment program of the UK's National Institute for Health Research (NIHR) which will be addressed separately in this report. This reference reports the results of the primary endpoint of the trial, the proportion of patients undergoing a repeat operation or further mastectomy within 6 months of randomisation, or a pathologically avoidable mastectomy at initial operation, and provide data about quality of life and health economic assessments.

Aim: The trial was designed to compare the efficacy of MRI and standard triple assessment with triple assessment alone in reduction of reoperation rates. Triple assessment was defined as clinical, radiological (X-ray mammography and ultrasound) and pathological (fine-needle aspiration cytology or core biopsy) assessment.

Population: Women aged 18 years or older with biopsy-proven primary breast cancer who were scheduled for wide local excision after triple assessment, who were not otherwise excluded, were eligible.

- Authors reported that most patients were 50 years or older, had breast density group 2 (2, 3, or 4 on the ACR BI-RADS scale), and were postmenopausal.
- breast cancer.

Randomization comments: Experiment (adaptive design or minimization used in place of randomization) which potentially may result in knowledge of impending allocation assignment. Minimization is not true randomization; however, a randomized element was utilized. A review of baseline characteristics is suggestive that the groups were balanced.

- Adequate concealment of allocation through use of telephone randomization system.

Performance comments:

- Not blinded, except for quality assessment of scan interpretation. 153 MRI scans (19%) were re-read.
- Standard protocols or guidelines were used for mammography, ultrasound, classification of lesions, histopathological assessment of excised specimens. A quality assurance process was used to ensure that MRI scans were completed in accordance with the technical needs of the trial protocol, and that scan interpretation was consistent between all participating centres. This process was completed by an independent radiologist, who was masked to the original MRI findings. Of the 19% of scans undergoing a quality assurance review, 8% (12 scan) were judged as being technically non-compliant, a subset of which were considered being misreported (3% or 5 scans). Sensitivity analyses were not deemed necessary as most of these came from centers with low recruitment which accounted for only 5% overall of the total number of scans.
- Some variation appears likely in defining "clear margin" as each participating physician participating consultant breast surgeon provided their local definition of a clear margin before starting recruitment. Local definitions were applied to both trial groups, and ranged from 0.5 to 5.0 mm for invasive disease and 1.0 to 10.0 mm for ductal carcinoma in situ.
- Patients were followed for at least 1 year.
- Authors acknowledge that, "Extent of experience of the radiologists is acknowledged as a potential limitation of our study, but this issue will always exist in real practice. Although analysis of our data showed a significant radiologist effect, the variation in data was probably attributable to differences between patients rather than between radiologists."

Analysis comments:

- Some adjustment was made for minimization factors, however further details are not provided, resulting in uncertain impact on study results. However, it appears possible that this was only done for a sensitivity analysis to

explore associations of factors such as breast density and surgeon with reoperation rates, (the latter two as being reported as having not been identified as being significantly associated with reoperation).

- One patient assigned to each arm was found lacking confirmation of informed consent and not included in the analysis. Overall loss less than 1 percent in each arm. Imputation for those lost to follow-up was "no primary endpoint event."
- Patients undergoing a mastectomy at initial operation because of patient decision alone were regarded
- as having a reoperation.
- Authors state that, "Effectiveness of imaging examined the agreement between predicted patient management established from results of MRI compared with management based on results of histopathological assessment of the excised specimen. Predicted patient management was based on raw data and calculated with special reference to: number and type (benign or malignant) of lesions detected; maximum diameter of all foci of invasive or in-situ carcinoma, or the sum of invasive and in-situ carcinoma present; and location and extent of additional tumours (localised, multifocal, or multicentric). DMEC definitions (pre-established criteria) were used to establish whether a change in surgical management from wide local excision to mastectomy was needed on the basis of results from both MRI and histopathology separately. With an assumption that histopathology was the gold standard, and regarding mastectomy to be a positive outcome and wide local excision to be negative, we calculated sensitivity, specificity, and positive and negative predictive values for the predicted management."

Diagnostic testing comments:

- Measures of test function for predicted management were calculated considering histopathology to be the gold standard, mastectomy to be a positive outcome and wide local excision to be a negative outcome.
- Median time from randomisation to MRI for patients assigned to receive MRI was 3 days (IQR 1–6), and from randomisation to initial surgery was 14 days (8–20) in this group and 13 days (8–18) in the group with no further imaging. For those undergoing a mastectomy in the MRI group, the median time from randomisation to surgery was 19 days (12–34), consisting of a median of 22 days (10–47) for those undergoing an additional biopsy before surgery and a median of 17 days (7–25) for those proceeding directly to mastectomy. An interval of 243 days between randomisation and surgery was recorded for one patient who underwent neoadjuvant chemotherapy. The protocol specified that an MRI scan should not delay surgery; therefore, only 2% of patients waited longer than 40 days between random assignment and surgery, and less than 1% more than 50 days.

Quality of life measurement comments:

- Instrument used was the EQ-5D which is reported to be a standardized and validated.

FINDINGS: 816 patients were randomly assigned to MRI and 807 to no MRI. Addition of MRI to conventional triple assessment was not significantly associated with reduced a reoperation rate, with 153 (19%) needing reoperation in the MRI group versus 156 (19%) in the no MRI group, (odds ratio 0.96, 95% CI 0.75 to 1.24; p=0.77).

RC:

- Absolute risk reduction for repeat operation or mastectomy at further operation within 6 months of randomisation, or a pathologically avoidable mastectomy at initial surgery, with a difference between the MRI and no MRI group of 0·58% (95% CI –3·24 to 4·40%).
- Measures of test function for MRI-predicted patient management were reported as—
    - Sensitivity 50.0% (95% CI 42.7 to 57.4)
    - Specificity 89.3% (95% CI 86.6 to 92.0%)
- Authors also report that, "Agreement in the staging of tumours between MRI and histopathology showed that all imaging modalities offer, at most, only some agreement with pathology, when taking into account the size of index lesion alone (κ values; ultrasound 0.46, 95% CI 0.41 to 0.50, X-ray mammography 0.45, 0.41 to 0.49, MRI 0.45, 0.39 to 0.50). However, when incorporating data from patients with ductal carcinoma in situ, agreement with ultrasound was poorer, with the 95% CIs around the weighted κ statistic almost entirely excluding those for MRI (κ values; ultrasound 0.38, 0.34 to 0.42, X-ray mammography 0.41, 0.37 to 0.46, MRI 0.48, 0.42 to 0.53)."
- Through modeling, authors attempted to assess a radiologist effect on the size of lesion and extent of disease as identified by MRI compared with histopathological results, but found no radiologist effect associated with differences in extent of disease. Rather, differences appeared to be attributable to differences in patients.
- Authors state that they identified no statistically significant difference due to tumor type, but caution that low rates of patients with lobular carcinoma (9%) may make these findings unreliable.
- Quality of life scores were reported as being similar between the two groups.

INTERPRETATION: Our findings are of benefit to the NHS because they show that MRI might be unnecessary in this population of patients to reduce repeat operation rates, and could assist in improved use of NHS services.

RC:

- Authors also state that, "These results emphasise the need to take biopsy samples of all lesions that might result in an alteration to the planned surgical procedure."
- Editorial raises questions—Citation: Morris EA. Should we dispense with preoperative breast MRI? Lancet. 2010 Feb 13;375(9714):528-30. PubMed PMID: 20159274. Morris points out—
    - The "extremely wide negative margins," stating that, "MRI might have little to add in mapping the area of tumor in this population. With smaller resection volumes with higher re-excision rates, the benefit of using MRI might well be greater."
    - Modifications in local surgical, pathological or radiologic practice were not tracked. Authors, however, state standards were used.
    - For 16 out of 58—or 27.6% —of mastectomies [in the MRI group], there was no pathological verification of disease. She further states that, "These pathologically avoidable mastectomies were counted in the reoperation rate, thus diminishing the effect of MRI."
    - A large number of patients were required by surgeons who recruited very few patients which could result in selection bias.
    - Postmenopausal patients were in the majority at 70% and may not be the ideal population to benefit from MRI.
    - Specialized centers with MRI experience have shown that preoperative MRI can decrease positive margin rates for invasive lobular cancer without increasing mastectomy rates, and therefore, preoperative staging with MRI in this group might be valid. [However, this study cited—Mann 10—was evaluated by us and was Delfini-graded BU to U and AHRQ-graded by us as high risk of bias.]
    - MRI images cancer not discoverable by other methods, resulting in the possibility of benefit in some populations.
    - COMICE does not fully answer whether preoperative breast MRI adds benefit as recurrence and overall survival were not examined.

Warner 08

Study Reference: Warner E, Messersmith H, Causer P, Eisen A, Shumak R, Plewes D. Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer. Ann Intern Med. 2008 May 6;148(9):671-9. Review. PubMed PMID: 18458280.

Abstract

Background: A sensitive and acceptable screening regimen for women at high risk for breast cancer is essential. Contrast enhanced magnetic resonance imaging (MRI) of the breast is highly sensitive for diagnosis of breast cancer but has variable specificity.

Purpose: To summarize the sensitivity, specificity, likelihood ratios, and posttest probability associated with adding MRI to annual mammography screening of women at very high risk for breast cancer.

Data Sources: English-language literature search of the MEDLINE, EMBASE, and Cochrane databases from January 1995 to September 2007, supplemented by hand searches of pertinent articles.

Study Selection: Prospective studies published after 1994 in which MRI and mammography (with or without additional tests) were used to screen women at very high risk for breast cancer.

Data Extraction: Methods and potential biases of studies were assessed by 2 reviewers, and data were extracted and entered into 2 X 2 tables that compared American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) scores of MRI plus mammography, mammography alone, or MRI alone with results of breast tissue biopsies.

Data Synthesis: Eleven relevant, prospective, nonrandomized studies that ranged from small single-center studies with only 1 round of patient screening to large multicenter studies with repeated rounds of annual screening were identified. Characteristics of women that varied across study samples included age range, history of breast cancer, and *BRCA1* or *BRCA2* mutation status. Studies used dynamic contrast-enhanced MRI with axial or coronal plane images (European studies) or sagittal images (North American studies) that were usually interpreted without knowledge of mammography results. **The summary negative likelihood ratio and the probability of a BI-RADS–suspicious lesion (given negative test findings and assuming a 2% pretest probability of disease) were 0.70 (95% CI, 0.59 to 0.82) and 1.4% (CI, 1.2% to 1.6%) for mammography alone and 0.14 (CI, 0.05 to 0.42) and 0.3% (CI, 0.1% to 0.8%) for the combination of MRI plus mammography, using a BI-RADS score of 4 or higher as the definition of positive.**

Limitations: Differences in patient population, center experience, and criteria for positive screening results led to between-study heterogeneity. Data on patients with nonfamilial high risk were limited, and no data were available on recurrence or survival.

Conclusion: Screening with both MRI and mammography might rule out cancerous lesions better than mammography alone in women who are known

Reviewer Evidence Rating:

Delfini Grade: Grade BU for Test Accuracy

AHRQ Rating: Medium Risk of Bias

Delfini Evidence Statement:

The evidence might be sufficient to use in making health care decisions; however, there remains sufficient uncertainty that the evidence cannot fully reach a Grade B and the uncertainty is not great enough to fully warrant a Grade U. Study quality is such that it appears likely that the evidence is sufficient to use in making health care decisions; however, there are some study issues that raise continued uncertainty. Health care decision-makers should be fully informed of the evidence quality.

Reviewer Comment: This meta-analysis used adequate methods for assessing studies for inclusion. Reported sensitivity of the combination of MRI and mammography ranged from 80% to 100%, compared with 25% to 59% for mammography alone. In every study except one, the specificity of MRI was lower than that of mammography; specificity of the combined tests ranged from 73% to 93%.

The combination of MRI and mammography with a BI-RADS score of 4 or higher as positive provided the best balance of performance in terms of all measures investigated (sensitivity, specificity, diagnostic odds ratios, likelihood ratios, and posttest probabilities). The summary negative likelihood ratio and probability of a BI-RADS–suspicious

lesion (given negative test findings and assuming a 2% pretest probability of disease) for the combination of MRI plus mammography were 0.14 and 0.3%, respectively, compared with 0.70 and 1.4% for mammography alone.

Note: The effectiveness of a screening test is demonstrated by showing that it reduces patient mortality. If there is evidence that it detects an increased number of cases of disease with a reduction in rates of advanced cancers in subsequent screening rounds it may be reasonable to conclude that the evidence is suggestive of efficacy. This meta-analysis did not provide evidence of reduction in advanced cancers or mortality. Therefore conclusions about the efficacy of MRI as a screening test in women with increased risk of breast cancer (in this meta-analysis defined as women with BRCA1 or BRCA2 or strong family history of breast cancer) must based on evidence of improved sensitivity together with assumptions about the benefits of early detection, considering previous evidence from studies of mammographic screening trials conducted in average risk populations who differ and whose breast cancers may differ significantly from women at higher risk. For example women in trials of average risk populations may be older and have different known and unknown prognostic variables. Breast cancers in younger high risk women may behave differently from those at average risk. The evidence is sufficient to conclude that the addition of MRI to mammography results in the increased detection of breast cancer cases and that the evidence is insufficient to conclude that mortality or morbidity is decreased.

Study Type

Systematic review and meta-analysis

Funding Source

The Program in Evidence-based Care is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of
Health and Long-Term Care through Cancer Care Ontario.

Aim

Details	To perform a systematic review of prospective studies in which women at very high risk for breast cancer were screened with both MRI and mammography. Authors sought to summarize the sensitivity, specificity, likelihood ratios, and posttest probability associated with combining these 2 tests.

Outcome Measures

Details	Sensitivity, specificity, likelihood ratios, and posttest probability associated with adding MRI to annual mammography screening of women at very high risk for breast cancer. Reference standard – biopsy proven breast cancer.

Population

Population: untested first-degree relative of a person with such a gene mutation; or having a family history consistent with a hereditary breast cancer syndrome, atypical or lobular carcinoma in situ on previous biopsy, or radiation therapy to chest (before age 30 years and at least 8 years previously).

N: After reviewing the titles and abstracts of 217 articles identified in the electronic search and removing duplicates, authors selected 40 for full-text review. Of these, they identified 11 articles describing 11 prospective studies comparing MRI with mammography.

::SECONDARY STUDY

Search Strategy

Details	Investigators searched EMBASE, MEDLINE, and the Cochrane Central Register of Controlled Trials to September 2007 by using subject and text word search terms for magnetic resonance imaging or MRI, breast cancer, and the concept of high risk.
	▪ No remarks

Critical Appraisal Methods

	Authors included prospective studies that examined use of MRI plus mammography, with or without ultrasonography and clinical breast examination, to screen women at very high risk for breast cancer. Studies had to report sensitivity, specificity, positive or negative predictive value, tumor stage, or survival and be published in a peer-reviewed journal. No minimum length of study follow-up was required. The target population consisted of women at high risk for breast cancer, defined as having a known mutation in *BRCA1*, *BRCA2*, or another gene associated with hereditary breast cancer; being an untested first-degree relative of a person with such a gene mutation; or having a family history consistent with a hereditary breast cancer syndrome, atypical or lobular carcinoma in situ on previous biopsy, or radiation therapy to chest (before age 30 years and at least 8 years previously). They included only English language studies because of lack of translation resources and only studies published after 1994 to exclude outdated technology. **Data Extraction and Analysis** Two reviewers independently abstracted all data. They did not numerically score the validity or quality of studies; however, they assessed the methodology and conduct of studies and paid particular attention to issues that might bias findings, such as double reading of images. They extracted data on patient population; additional screening tests; MRI technique; reporting of blinding of image assessment; compliance, drop-out rates and reasons, and completeness of follow-up; total number of centers, patients, and screens; number of prevalent, incident, and interval cases of cancer detected; number of in situ versus invasive tumors detected, with size and nodal status of the latter; and reported sensitivity and specificity. They extracted raw data to tabulate the number of false-positive, false-negative, true-positive, and true-negative screening results for mammography, MRI, and the combination of the 2 tests. After study review, authors concluded that conducting a meta-analysis without regard for the American College of Radiology Breast Imaging Reporting and Data System (BIRADS) score used in each study to classify a positive test would be inappropriate and misleading. They therefore conducted all of the analyses separately whenever possible, using BI-RADS scores of 0 (indeterminate), 3 (short follow- up interval required), 4 (suspicious), and 5 (highly suspicious and requiring biopsy) as the definition of positive and then using only BI-RADS scores of 4 or 5 as positive, even if 1 of these criteria was not chosen a priori. They assumed a 2% prevalence from the pooled study results. They assessed the heterogeneity of these measures by using both a chi-square test for heterogeneity and the $I2$ value; they considered a P value less than 0.1 on chi-square test or an $I2$ value greater than 50% to be evidence of statistical heterogeneity. To allow inclusion of studies with zero patients in a cell of the contingency table, they added 0.5 to those cells. In all studies, mammography and MRI were conducted within 90 days of each other and usually on the same day. In studies with 2 or more rounds of screening, the screening interval was 1 year. All studies considered biopsy-confirmed cancer the definitive positive result for sensitivity calculations. However, some considered BI-RADS scores of 3, 4, or 5 to be positive, whereas others considered only BI-RADS scores of 4 or 5 to be positive.

Blinding Threat	▪ Outcome assessors were blinded to other tests in 9 of 11 studies. (Trecate 06 and Harman 04 did not report blinding.)
Missing Values in Results	Threat. Not reported.
Heterogeneity Threat	Studies were heterogeneous in terms of patient population, sample size, number of screening examinations, and center experience. Many of the results were associated with considerable statistical heterogeneity (chi-square P value <0.1)
Other Threats	To allow inclusion of studies with zero patients in a cell of the contingency table, they added 0.5 to those cells.

Meta-Analysis Results

Reported sensitivity of the combination of MRI and mammography ranged from 80% to 100%, compared with 25% to 59% for mammography alone. In every study except one, the specificity of MRI was lower than that of mammography; specificity of the combined tests ranged from 73% to 93%.

The summary negative likelihood ratio and the probability of a BI-RADS–suspicious lesion (given negative test findings
and assuming a 2% pretest probability of disease) were 0.70 (95% CI, 0.59 to 0.82) and 1.4% (CI, 1.2% to 1.6%) for mammography alone and 0.14 (CI, 0.05 to 0.42) and 0.3% (CI, 0.1% to 0.8%) for the combination of MRI plus mammography, using a BI-RADS score of 4 or higher as the definition of positive.

Details are provided by BI-RADS Cutoff values in the chart below but quantitative summary estimates are somewhat uncertain because the studies were heterogeneous in terms of patient population, sample size, number of screening examinations, and center experience.

:: Table: Sensitivity / Specificity Breast Cancer Detection in High Risk Women (Warner 08 Meta-analysis)

Screening Strategy, BI-RADS* Cutoff Value	Diagnostic Odds Ratio (95% CI)	Sensitivity (95% CI), %	Specificity (95% CI), %	Positive Likelihood Ratio (95% CI)	Negative Likelihood Ratio (95% CI)
Mammography ≥3 ≥4	 14.7 (6.1 to 35.6) 38.5 (15.9 to 93.3)	 39 (37 to 41) 32 (23 to 41)	 94.7 (93.0 to 96.5) 98.5 (97.8 to 99.2)	 8.7 (4.4 to 17.5) 24.8 (11.6 to 53.0)	 0.64 (0.55 to 0.75) 0.70 (0.59 to 0.82)
MRI ≥3 ≥4	 18.3 (11.7 to 28.7) 88.7 (34.6 to 227.5)	 77 (70 to 84) 75 (62 to 88)	 86.3 (80.9 to 91.7) 96.1 (94.8 to 97.4)	 4.2 (3.0 to 5.9) 16.6 (11.1 to 25.0)	 0.29 (0.21 to 0.41) 0.22 (0.12 to 0.43)
Mammography and MRI ≥3 ≥4	 45.9 (17.5 to 120.9) 124.8 (36.4 to 427.4)	 94 (90 to 97) 84 (70 to 97)	 77.2 (74.7 to 79.7) 95.2 (93.7 to 96.6)	 4.1 (3.6 to 4.7) 16.4 (11.1 to 24.1)	 0.09 (0.04 to 0.23) 0.14 (0.05 to 0.42)

*BI-RADS _ Breast Imaging Reporting and Data System

:: Table: Results from 11 Individual Studies Reported in Warner 08

Notes

- Number: Alphabetically arranged; reference number applies to the order in this table only (i.e., is not tied to **References**)

#	Author, Year, Population, Screening Strategy for Studies Included in Warner 08	Sensitivity Specificity PPV Mammography	Sensitivity Specificity PPV MRI	Sensitivity Specificity PPV MRI + Mammography	Cases Breast Ca / Total Examinations (Some cases may have been detected by US)
1.	Hagen 07 N=491 Mean age 41 No risk criteria BI-RADS 3-5	Sensitivity 32% Specificity NR PPV NR	Sensitivity 68% Specificity NR PPV NR	Sensitivity 80% Specificity NR PPV NR	25/867=2.9%
2.	Hartman 04 N=41 High Family Risk (>1%/yr) Median age 42.5 BI-RADS 4 or 5 Blinding not reported	Sensitivity 0% Specificity NR PPV NR	Sensitivity 100% Specificity 75% PPV 9%	Sensitivity 100% Specificity NR PPV NR	1/41=2.4%
3.	Kriege et al.,2004 N=1909 Mean age 40 years High familial risk (≥20% lifetime) BI-RADS score 4 or 5	Sensitivity 33% Specificity 99% PPV 27%	Sensitivity 64% Specificity 96% PPV 16%	Sensitivity NR Specificity NR PPV NR	45/4169=1.1%
4.	Kuhl 2005 N=529 Median age 40 years (range 27 to 59 years) Prior history of breast cancer: 26% High familial risk (≥15% lifetime) Conventional testing = mammography + ultrasound BI-RADS score 4 or 5	Sensitivity 32% Specificity 97% PPV 24%	Sensitivity 91% Specificity 97% PPV 50%	Sensitivity 93% Specificity 96% PPV 42%	43/1452=3%
5.	Leach 2005 (magnetic resonance imaging breast screening (MARIBS)) United Kingdom 22 sites 1997 to 2004 N=649 Median age 40 years (range 31 to 55 years) High familial risk (≥0.9% per year) Prior history of breast cancer: 0% BI-RADS score 4 or 5	Sensitivity 14% Specificity 98% PPV 15%	Sensitivity 51% Specificity 96% PPV 21%	Sensitivity 60% Specificity 95% PPV 20%	35/1881=1.9%
6.	Lehman 07 N=171 Mean age 45 High Risk (>25% lifetime risk)	Sensitivity 33% Specificity 91% PPV 12%	Sensitivity 100% Specificity 79% PPV 15%	Sensitivity 100% Specificity 73% PPV 12%	6/171=3.5%
7.	Lehman 2005 (International Breast MRI Consortium Working Group (IBMC)) USA, Canada 13 sites 1999 to 2002 N=367 Mean age 45 years High familial risk (≥25% lifetime) Prior history of breast cancer: 10% Conventional testing = mammography BI-RADS score 4 or 5	Sensitivity 25% Specificity NR PPV 25%	Sensitivity 100% Specificity NR PPV 17%	NR	3/367 additional cases=0.8%

#	Author, Year, Population, Screening Strategy for Studies Included in Warner 08	Sensitivity Specificity PPV Mammography	Sensitivity Specificity PPV MRI	Sensitivity Specificity PPV MRI + Mammography	Cases Breast Ca / Total Examinations (Some cases may have been detected by US)
8.	Sardanelli 2007 N=278 Mean age 46 years (range 25 to 79 years) High familial risk Prior history of breast cancer: 39% Conventional testing = mammography + ultrasound + CBE	Sensitivity 59% Specificity 99% PPV 77%	Sensitivity 94% Specificity 98% PPV 63%	Sensitivity 100% Specificity NR PPV NR	18/377=4.7%
9.	Trecate 2006 N=116 High Familial Risk Ages 23-81 BI-RADS 4 or 5 Blinding not reported	Sensitivity 33% Specificity 100% PPV 100%	Sensitivity 100% Specificity 97% PPV 79%	Sensitivity 100% Specificity 97% PPV 79%	12/116=10.3%
10.	Warner 2001 N=196 Mean age 43 High familial risk (≥25% lifetime) BI-RADS score 4 or 5	Sensitivity 43% Specificity 99% PPV 55%	Sensitivity 86% Specificity 91% PPV 26%	Sensitivity 100% Specificity NR PPV NR	7/196=3.6%
11.	Warner 2004 N=236 Median age: 47 years Prior history of breast cancer: 30% Risk classification BRCA1/2 mutation carriers 100% No family history criteria Conventional testing = mammography + ultrasound + CBE	Sensitivity 36% Specificity 100% PPV 88%	Sensitivity 77% Specificity 95% PPV 46%	Sensitivity 86% Specificity 95% PPV 48%	22/457=4.8%

Investigators did not identify any studies that compared patient outcomes or stage shifts in high risk women screened with and without MRI**.**

Warren 09
MRI Technical Considerations
Systematic Review

Citation: Warren R, Ciatto S, Macaskill P, Black R, Houssami N. Technical aspects of breast MRI--do they affect outcomes? Eur Radiol. 2009 Jul;19(7):1629-38. Epub 2009 Feb 27. Review. PubMed PMID: 19247664.

Manufacture Involvement: No

Reviewer Grade
Delfini Grade: BU
AHRQ Grade: Medium Risk of Bias

Delfini Evidence Statement:
The evidence might be sufficient to use in making health care decisions; however, there remains sufficient uncertainty that the evidence cannot fully reach a Grade B and the uncertainty is not great enough to fully warrant a Grade U. Study quality is such that it appears likely that the evidence is sufficient to use in making health care decisions; however, there are some study issues that raise continued uncertainty. Health care decision-makers should be fully informed of the evidence quality.

PUBLISHED ABSTRACT SECTIONS WITH REVIEWER COMMENTS (RC)

PURPOSE: To assess the effect of technical aspects of MRI on diagnostic performance.

RC:
- Ipsilateral breast with cancer diagnosis.

MATERIALS AND METHODS: Where technical parameters were complete, authors examined their effect on summary ROC models, and the TP:FP ratio and PPV, using random-effects logistic regression analysis. Analyzed technical parameters: year of study, slice thickness, and repetitions after contrast-medium injection.

RC:
Population
A total of 2,801 breasts in 19 publications

SEE SECONDARY STUDY DETAILS BELOW THIS TABLE FOR MORE DETAILS AND THREATS TO VALIDITY

RESULTS: None were associated with TP/FP ratio. Tesla strength was reported in 2,801 cases. Other key information was omitted including whether both breasts were examined for 1683 (60%), position of the patient in 1,375 (49%), and imaging planes used in 688 (25%). Contrast agent and dose were reported for 2,646 (95%) breasts. Reporting technique was inconsistently reported. Single radiology reports were found in 1,637 (58%) cases, double in 347 (12.4%), and in 960 (34%) knowledge of mammography or ultrasound findings was not stated. Slice thickness, number of sequences after contrast medium, and year of study did not show significant performance differences. Other technical information was deficient.

RC:
Problem: One or more of the following apply
- Poor reporting noted by authors.
- Based on: Houssami N, Ciatto S, Macaskill P, Lord SJ, Warren RM, Dixon JM, Irwig L. Accuracy and surgical impact of magnetic resonance imaging in breast cancer staging: systematic review and meta-analysis in detection of multifocal and multicentric cancer. J Clin Oncol. 2008 Jul 1;26(19):3248-58. Epub 2008 May 12. Review. PubMed PMID: 18474876.

CONCLUSION: Agree with authors.

RC:
Selected Authors' Conclusions:
There is an urgent need to improve the quality of reporting technical details of breast MRI studies.

Weinstein 09
MRI: Screening
Citation: Weinstein SP, Localio AR, Conant EF, Rosen M, Thomas KM, Schnall MD. Multimodality screening of high-risk women: a prospective cohort study. J Clin Oncol. 2009 Dec 20;27(36):6124-8. Epub 2009 Nov 2. PubMed MID: 19884532; PubMed Central PMCID: PMC2793033.
Manufacture Involvement: No
Reviewer Grade
Delfini Grade: BU
AHRQ Grade: Medium risk of bias

Delfini Evidence Statement:
The evidence might be sufficient to use in making health care decisions; however, there remains sufficient uncertainty that the evidence cannot fully reach a Grade B and the uncertainty is not great enough to fully warrant a Grade U. Study quality is such that it appears likely that the evidence is sufficient to use in making health care decisions; however, there are some study issues that raise continued uncertainty. Health care decision-makers should be fully informed of the evidence quality.

PUBLISHED ABSTRACT SECTIONS (WHITE) WITH REVIEWER COMMENTS & KEY POINTS OF STUDY (RC IN GREY)

PURPOSE: Mammography has been established as the primary imaging screening method for breast cancer; however, the sensitivity of mammography is limited, especially in women with dense breast tissue. Given the limitations of mammography, interest has developed in alternative screening techniques. This interest has led to numerous studies reporting mammographically occult breast cancers detected on magnetic resonance imaging (MRI) or ultrasound. In addition, digital mammography was shown to be more sensitive than film mammography in selected populations. Our goal was to prospectively compare cancer detection of digital mammography (DM), whole-breast ultrasound (WBUS), and contrast-enhanced MRI in a high-risk screening population previously screened negative by film screen mammogram (FSM).

METHODS: During a 2-year period, 609 asymptomatic high-risk women with nonactionable FSM examinations presented for a prospective multimodality screening consisting of DM, WBUS, and MRI. The FSM examinations were reinterpreted by study radiologists. Patients had benign or no suspicious findings on clinical examination. The cancer yield by modality was evaluated.

RC:
- Observational study

Population
- Women between ages of 25 and 80 considered high risk for breast cancer based on based on any of the following were considered eligible: positive test for a mutation in BRCA1 or BRCA2, >/=25% lifetime risk based on the Claus or Gail models, previous diagnosis of lobular carcinoma in situ or atypical hyperplasia (atypical ductal hyperplasia or atypical lobular hyperplasia), history of chest wall radiation before puberty, and a recent diagnosis of breast cancer in the contralateral breast.
- In addition, as part of entry criteria, all women had a nonactionable mammogram within 180 days of enrollment as well as no suspicious findings on clinical examination. For purposes of enrollment, a nonactionable mammogram was defined as a Breast Imaging Reporting and Data System (BIRADS) score of 1 or 2, a resolved BIRADS score of 0 or 3, or a BIRADS score of 4 associated with a biopsy negative for cancer based on interpretations performed as part of routine clinical care.
- Median age was 49 years, ranging from 27 to 81.

Methods
- Women were screened with all modalities on the same day
- In participants with recent diagnosis of breast cancer, only the data from the cancer-free breast were included in the study.
- All lesions receiving a consensus BIRADS rating of 4 or higher were recommended for biopsy. Following through on the biopsy recommendation was at the discretion of the patients' primary referring clinician.
- All patients were clinically followed for 2 years to establish cancer and vital status, after which they were considered negative if negative follow-up in that time.

Blinding
- Images were initially interpreted by different radiologists, all of whom were subspeciality trained and with

extensive experience

- WBUS and MRI were assumed to be adjunctive to mammography, and DM would be a stand-alone modality. Therefore, WBUS and MRI were interpreted with access to FSM images and reports but otherwise blinded to each other and the DM. The DM was interpreted with clinical history, but blinded to all other imaging information including FSM and the FSM report. The radiologist who performed the screening ultrasound examination also reinterpreted the entry FSM for study purposes. This initial set of interpretations is referred to as the "blinded modality interpretations," and was used as the primary data source for analysis Immediately after the examinations and blinded interpretations, a conference of the three study radiologists was held to review the findings of all modalities in an unblinded (to the other modalities) fashion. All imaging findings detected by each imaging modality were discussed, and consistent indexing of findings was developed across all modalities. The reader of each modality then individually reinterpreted his or her assigned modality representing the unblinded modality interpretation. On review of all the imaging modalities, by consensus, all lesions were assigned a final consensus (considering the combined information from all modalities) BIRADS5 rating and a percent likelihood of malignancy. Findings that were assigned BIRADS 0 on the blinded interpretations were either resolved by correlation with other modalities during the consensus conference or with additional projections performed on another day or were classified based on percent likelihood of malignancy using the BIRADS scale.
- There is no specific mention of how blinding occurred.

RESULTS: Twenty cancers were diagnosed in 18 patients (nine ductal carcinomas in situ and 11 invasive breast cancers). The overall cancer yield on a per-patient basis was 3.0% (18 of 609 patients). The cancer yield by modality was 1.0% for FSM (six of 597 women), 1.2% for DM (seven of 569 women), 0.53% for WBUS (three of 567 women), and 2.1% for MRI (12 of 571 women). Of the 20 cancers detected, some were only detected on one imaging modality (FSM, n = 1; DM, n = 3; WBUS, n = 1; and MRI, n = 8).

RC:

- A person was not counted in an analysis for a particular modality if no images were obtained using that modality.
- If a modality identified a lesion as actionable (positive) but another lesion was eventually found to be malignant, then at the patient level, this modality was scored as having missed a cancer. The cancer yield of each modality was calculated as the number of patients with a positive screen for that modality corresponding to a cancer diagnosis divided by the total patients imaged by that modality.
- Of 612 women enrolled, 609 were included in the analysis (99.5%).

CONCLUSION: The addition of MRI to mammography in the high-risk group has the greatest potential to detect additional mammographically occult cancers. The incremental cancer yield of WBUS and DM is much less.

RC:

- Prospective observational diagnostic study with some question about adequate blinding.
- Useful information.

V. REFERENCES

Notes

- References are alphabetically arranged; reference number applies to the order in this table only.

Number	Abbreviated Reference	Citation
30.	Berg 08	Berg WA, Blume JD, Cormack JB, Mendelson EB, Lehrer D, Böhm-Vélez M, Pisano ED, Jong RA, Evans WP, Morton MJ, Mahoney MC, Larsen LH, Barr RG, Farria DM, Marques HS, Boparai K; ACRIN 6666 Investigators. Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. JAMA. 2008 May 14;299(18):2151-63. Erratum in: JAMA. 2010 Apr 21;303(15):1482. PubMed PMID: 18477782; PubMed Central PMCID: PMC2718688.
31.	Brennan 09	Brennan ME, Houssami N, Lord S, Macaskill P, Irwig L, Dixon JM, Warren RM, Ciatto S. Magnetic resonance imaging screening of the contralateral breast in women with newly diagnosed breast cancer: systematic review and meta-analysis of incremental cancer detection and impact on surgical management. J Clin Oncol. 2009 Nov 20;27(33):5640-9. Epub 2009 Oct 5. Review. PubMed PMID: 19805685.
32.	Brewer 07	Brewer NT, Salz T, Lillie SE. Systematic review: the long-term effects of false-positive mammograms. Ann Intern Med. 2007 Apr 3;146(7):502-10. Review. PubMed PMID: 17404352.
33.	Chen 08	Chen MM, Coakley FV, Kaimal A, Laros RK Jr. Guidelines for computed tomography and magnetic resonance imaging use during pregnancy and lactation. Obstet Gynecol. 2008 Aug;112(2 Pt 1):333-40. PubMed PMID: 18669732.
34.	Essink-Bot 06	Essink-Bot ML, Rijnsburger AJ, van Dooren S, de Koning HJ, Seynaeve C. Women's acceptance of MRI in breast cancer surveillance because of a familial or genetic predisposition. Breast. 2006 Oct;15(5):673-6. Epub 2006 Mar 23. PubMed PMID: 16556497.
35.	Feig 04	Feig SA. Adverse effects of screening mammography. Radiol Clin North Am. 2004 Sep;42(5):807-19, v. Review. PubMed PMID: 15337417.
36.	Fischer 04	Fischer U, Zachariae O, Baum F, et al: The influence of preoperative MRI of the breasts on recurrence rate in patients with breast cancer. EurRadiol 14:1725-1731, 2004.
37.	Hoshaw 01	Hoshaw SJ, Klein PJ, Clark BD, Cook RR, Perkins LL. Breast implants and cancer: causation, delayed detection, and survival. Plast Reconstr Surg. 2001 May;107(6):1393-407. PubMed PMID: 11335807.
38.	Houssami 08	Houssami N, Ciatto S, Macaskill P, Lord SJ, Warren RM, Dixon JM, Irwig L. Accuracy and surgical impact of magnetic resonance imaging in breast cancer staging: systematic review and meta-analysis in detection of multifocal and multicentric cancer. J Clin Oncol. 2008 Jul 1;26(19):3248-58. Epub 2008 May 12. Review. PubMed PMID: 18474876.
39.	Kuhl 10	Kuhl C, Weigel S, Schrading S, Arand B, Bieling H, König R, Tombach B, Leutner C, Rieber-Brambs A, Nordhoff D, Heindel W, Reiser M, Schild HH. Prospective multicenter cohort study to refine management recommendations for women at elevated familial risk of breast cancer: the EVA trial. J Clin Oncol. 2010 Mar 20;28(9):1450-7. Epub 2010 Feb 22. PubMed PMID: 20177029.
40.	Lee 10	Lee JM, McMahon PM, Kong CY, Kopans DB, Ryan PD, Ozanne EM, Halpern EF, Gazelle GS. Cost-effectiveness of breast MR imaging and screen-film mammography for screening BRCA1 gene mutation carriers. Radiology. 2010 Mar;254(3):793-800. PubMed PMID: 20177093; PubMed Central PMCID: PMC2826703.

Number	Abbreviated Reference	Citation
41.	Lehman 07	Lehman CD, Gatsonis C, Kuhl CK, Hendrick RE, Pisano ED, Hanna L, Peacock S, Smazal SF, Maki DD, Julian TB, DePeri ER, Bluemke DA, Schnall MD; ACRIN Trial 6667 Investigators Group. MRI evaluation of the contralateral breast in women with recently diagnosed breast cancer. N Engl J Med. 2007 Mar 29;356(13):1295-303. Epub 2007 Mar 28. PubMed PMID: 17392300.
42.	Lim 10	Lim HI, Choi JH, Yang JH, Han BK, Lee JE, Lee SK, Kim WW, Kim S, Kim JS, Kim JH, Choe JH, Cho EY, Kang SS, Shin JH, Ko EY, Kim SW, Nam SJ. Does pre-operative breast magnetic resonance imaging in addition to mammography and breast ultrasonography change the operative management of breast carcinoma? Breast Cancer Res Treat. 2010 Jan;119(1):163-7. PubMed PMID: 19760039.
43.	Lord 07	Lord SJ, Lei W, Craft P, Cawson JN, Morris I, Walleser S, Griffiths A, Parker S, Houssami N. A systematic review of the effectiveness of magnetic resonance imaging (MRI) as an addition to mammography and ultrasound in screening young women at high risk of breast cancer. Eur J Cancer. 2007 Sep;43(13):1905-17. Epub 2007 Aug 2. Review. PubMed PMID: 17681781
44.	Mann 10	Mann RM, Loo CE, Wobbes T, Bult P, Barentsz JO, Gilhuijs KG, Boetes C. The impact of preoperative breast MRI on the re-excision rate in invasive lobular carcinoma of the breast. Breast Cancer Res Treat. 2010 Jan;119(2):415-22. PubMed PMID: 19885731.
45.	O'Neill 08	O'Neill SM, Rubinstein WS, Sener SF, Weissman SM, Newlin AC, West DK, Ecanow DB, Rademaker AW, Edelman RR. Psychological impact of recall in high-risk breast MRI screening. Breast Cancer Res Treat. 2009 May;115(2):365-71. Epub 2008 Jul 26. PubMed PMID: 18661230.
46.	Pengel 09	Pengel KE, Loo CE, Teertstra HJ, Muller SH, Wesseling J, Peterse JL, Bartelink H, Rutgers EJ, Gilhuijs KG. The impact of preoperative MRI on breast-conserving surgery of invasive cancer: a comparative cohort study. Breast Cancer Res Treat. 2009 Jul;116(1):161-9. Epub 2008 Sep 21. PubMed PMID: 18807269.
47.	Perazella 07	Perazella MA, Rodby RA. Gadolinium use in patients with kidney disease: a cause for concern. Semin Dial. 2007 May-Jun;20(3):179-85. Review. PubMed PMID: 17555477.
48.	Plevritis 06	Plevritis SK, Kurian AW, Sigal BM, Daniel BL, Ikeda DM, Stockdale FE, Garber AM. Cost-effectiveness of screening BRCA1/2 mutation carriers with breast magnetic resonance imaging. JAMA. 2006 May 24;295(20):2374-84. PubMed PMID: 16720823.
49.	Sardanelli 04	Sardanelli F, Giuseppetti GM, Panizza P, Bazzocchi M, Fausto A, Simonetti G, Lattanzio V, Del Maschio A; Italian Trial for Breast MR in Multifocal/Multicentric Cancer. Sensitivity of MRI versus mammography for detecting foci of multifocal, multicentric breast cancer in Fatty and dense breasts using the whole-breast pathologic examination as a gold standard. AJR Am J Roentgenol. 2004 Oct;183(4):1149-57. PubMed PMID: 15385322.
50.	Schwartz 00	Schwartz LM , Woloshin S , Sox HC , Fischhoff B , Welch HG . US women's attitudes to false positive mammography results and detection of ductal carcinoma in situ: cross sectional survey . BMJ 2000 ; 320 : 1635 – 1640.
51.	Scomersi 10	Scomersi S, Urbani M, Tonutti M, Zanconati F, Bortul M. Role of magnetic resonance imaging in managing selected women with newly diagnosed breast cancer. Breast. 2010 Apr;19(2):115-9. Epub 2010 Jan 27. PubMed PMID: 20106663.
52.	Shellock 06	Shellock FG, Parker JR, Pirovano G, Shen N, Venetianer C, Kirchin MA, Spinazzi A. Safety characteristics of gadobenate dimeglumine: clinical experience from intra- and interindividual comparison studies with gadopentetate dimeglumine. J Magn Reson Imaging. 2006 Dec;24(6):1378-85. Erratum in: J Magn Reson Imaging. 2007 Jul;26(1):217. PubMed PMID: 17078095.

Number	Abbreviated Reference	Citation
53.	Solin 08	Solin LJ, Orel SG, Hwang WT, Harris EE, Schnall MD. Relationship of breast magnetic resonance imaging to outcome after breast-conservation treatment with radiation for women with early-stage invasive breast carcinoma or ductal carcinoma in situ. J Clin Oncol. 2008 Jan 20;26(3):386-91. PubMed PMID: 18202414
54.	Taneja 09	Taneja C, Edelsberg J, Weycker D, Guo A, Oster G, Weinreb J. Cost effectiveness of breast cancer screening with contrast-enhanced MRI in high-risk women. J Am Coll Radiol. 2009 Mar;6(3):171-9. PubMed PMID: 19248993.
55.	Turnbull 10	Turnbull L, Brown S, Harvey I, Olivier C, Drew P, Napp V, Hanby A, Brown J. Comparative effectiveness of MRI in breast cancer (COMICE) trial: a randomised controlled trial. Lancet. 2010 Feb 13;375(9714):563-71. PubMed PMID: 20159292.
56.	Warner 08	Warner E, Messersmith H, Causer P, Eisen A, Shumak R, Plewes D. Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer. Ann Intern Med. 2008 May 6;148(9):671-9. Review. PubMed PMID: 18458280.
57.	Warren 09	Warren R, Ciatto S, Macaskill P, Black R, Houssami N. Technical aspects of breast MRI--do they affect outcomes? Eur Radiol. 2009 Jul;19(7):1629-38. Epub 2009 Feb 27. Review. PubMed PMID: 19247664.
58.	Weinstein 09	Weinstein SP, Localio AR, Conant EF, Rosen M, Thomas KM, Schnall MD. Multimodality screening of high-risk women: a prospective cohort study. J Clin Oncol. 2009 Dec 20;27(36):6124-8. Epub 2009 Nov 2. PubMed PMID: 19884532; PubMed Central PMCID: PMC2793033.